

Opioid Agonists and Antagonists

MORPHINE AND RELATED OPIOIDS

History

- first undisputed reference to "poppy juice" is found in the writings of *Theophrastus* in the third century B.C.
- the word opium being derived from the Greek word for "juice"
- the drug being obtained from the juice of the poppy *Papaver somniferum*
- Arabian physicians were well versed in its uses and introduced the plant to the Orient
- Paracelsus, circa 1500, is credited with repopularising the drug in Europe, where it had fallen out of favor due to toxicity
- in the 18th century *opium* smoking became popular in the Orient and its ready availability in Europe led to considerable abuse
- opium contains more than 20 alkaloids and in 1806, Sertürner isolated a pure substance in opium, which he named *morphine*, after Morpheus, the Greek god of dreams
- isolation of other alkaloids soon followed, *codeine* in 1832 and *papaverine* in 1848
- by the middle of the 19th century, use of the pure alkaloids rather than crude opium was becoming widespread
- the problems of widespread *addiction* led to the search for a morphine antagonist, and in 1951 *nalorphine* was used in the R_x of morphine overdose
- at the same time, the analgesic effects stimulated the development of a number of new drugs, including *naloxone*, pentazocine, butorphanol etc.
- by 1967, researchers had concluded that the complex interactions and differences between morphine and its derivatives could only be explained by the existence of more than one receptor type → *receptor dualism*, Martin (1967)
- in 1973, following an approach developed by Goldstein, 3 groups of workers described saturable, stereospecific binding sites for opiate drugs
- in 1975, the *enkephalin* pentapeptides were isolated from pig brain
- since then researchers have shown that there are three distinct families of *endogenous opioid* peptides and multiple categories of opioid receptors

Classification	
<i>Natural Alkaloids of Opium</i>	
• phenanthrenes	morphine, codeine, thebaine
• benzyloisoquinolines	papaverine, noscapine
<i>Semi-synthetic Derivatives</i>	diacetylmorphine (heroin) hydromorphone, oxymorphone hydrocodone, oxycodone
<i>Synthetic Derivatives</i>	
• phenylpiperidines	pethidine, fentanyl, alfentanil, sufentanil
• benzmorphans	pentazocine, phenazocine, cyclazocine
• propionanilides	methadone
• morphinans	levorphanol

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Structure Activity Relationship

- detailed analysis of opioid stereospecificity has led to a hypothetical three dimensional model of the opiate receptor
- the majority of compounds exist as complex structures, usually with a number of optical isomers, of which only the *l-isomer* is usually active
- the structural similarities within most in this class include,
 - a. structure conforms to a "T-shape"
 - b. a tertiary, positively charged *basic nitrogen*
 - c. a quaternary carbon, C₁₃ in morphine,
 - i. separated from the basic nitrogen by an ethane (-CH₂--CH₂-) chain
 - ii. attached to a phenyl group (phenol, ketone)
 - d. the presence of an aromatic ring, whose centre is 0.455 nm from the nitrogen atom
- short chain alkyl group substitution at the basic nitrogen results in agents with mixed agonist-antagonist actions
- additional hydroxylation at C₁₄ results in an *antagonist* agent
- phenylalanine and tyrosine form important structural elements of the endogenous opioids

Opioid Receptors

- following their description in 1973, and that of the endogenous opioids in 1975, a large amount of data was collected
- this provided a degree of contradictory information which could only be explained by the presence of a number of opioid receptors
- the evidence for the existence of multiple opioid receptors includes,
 - a. different families of opioids display different *pharmacological profiles*
 - b. they display different *rank order of potencies* in different bioassays
 - c. the *apparent K_d' for naloxone* differs in the same bioassay with different agonists
 - d. *cross tolerance* does not necessarily occur
 - e. agonists display differential responses after alkylation of receptor sites
 - f. the rank order of *displacement potency* varies according to the opioid already bound to the receptor
- further, the concentration and proportion of receptor subclasses changes with *time* and under the influence of an *agonist drug*

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- except for some types of σ -receptors, **naloxone** binds with high affinity to **all** opioid receptors
- however, its affinity for μ -receptors is generally ~ 10 fold greater
- the discovery of δ -receptors was essentially the result of work with met- & leu-enkephalin
- however, since no exogenous opioid has the same spectrum of activity as either of these substances, the knowledge of pharmacological effects of their stimulation is lacking
- therefore, the actions of opioids are generally described with reference to only 3 types of receptors → μ , κ , & σ

- on the basis of these receptors, drugs can be divided into four groups,
 - a. agonists
 - b. antagonists
 - c. agonist-antagonists
 - d. partial agonists

Agent Class	Example	Action
Agonist	<ul style="list-style-type: none"> • morphine • fentanyl • pethidine 	activation of all receptor subclasses, though, with different affinities
Antagonist	<ul style="list-style-type: none"> • naloxone 	devoid of activity at all receptor classes
Agonist-Antagonist	<ul style="list-style-type: none"> • nalorphine • pentazocine 	agonist activity at one type and antagonist activity at another
Partial Agonist	<ul style="list-style-type: none"> • buprenorphine 	activity at one or more, but not all receptor types

- with regard to **partial agonists**, receptor theory states that drugs have two independent properties at receptor sites,
 - a. **affinity**
 - the ability, or avidity to bind to the receptor
 - proportional to the association rate constant, K_a
 - b. **efficacy**
 - or, **intrinsic activity**, and is the ability of the D-R complex to initiate a pharmacological effect

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- drugs that produce a less than maximal response and, therefore, have a low intrinsic activity are called *partial agonists*
- these drugs display certain pharmacological features,
 - a. the *slope* of the dose-response curve is less than that of a full agonist
 - b. the dose response curve exhibits a *ceiling* with the maximal response below that obtainable by a full agonist
 - c. partial agonists are able to *antagonise* the effects of large doses of full agonists

Characteristics of Opioid Receptors			
Receptor	Tissue Bioassay	Agonists	Major Actions
mu₁	guinea pig ileum	<i>morphine</i> phenylpiperidines	<ul style="list-style-type: none"> • analgesia • bradycardia • sedation
mu₂	guinea pig ileum	<i>morphine</i> phenylpiperidines	<ul style="list-style-type: none"> • respiratory depression • euphoria • physical dependence
delta	mouse vas deferens	<i>dAla-dLeu-Enk</i> "DADLE"	<ul style="list-style-type: none"> • analgesia-weak • respiratory depression
kappa	rabbit vas deferens	<i>ketocyclazocine</i> dynorphin nalbuphine butorphanol	<ul style="list-style-type: none"> • analgesia-weak • respiratory depression • sedation
sigma		<i>SKF-10,047</i> pentazocine	<ul style="list-style-type: none"> • dysphoria -delerium • hallucinations • tachycardia • hypertension
epsilon	rat vas deferens	<i>b-endorphin</i>	<ul style="list-style-type: none"> • stress response • acupuncture

Opioid Agonists and Antagonists

Receptor Characteristics		
mu	μ_1	<ul style="list-style-type: none"> • spinal & supraspinal analgesia • euphoria • physical dependence • catalepsy • miosis • hypothermia • prolactin release • inhibition of testosterone
	μ_2	<ul style="list-style-type: none"> • respiratory depression • morphine induced bradycardia • inhibition of GIT motility
delta	δ	<ul style="list-style-type: none"> • spinal analgesia • dependence without drug seeking behaviour • stress-induced analgesia • endotoxic shock • hypotension • hyperthermia • GH release
kappa	κ	<ul style="list-style-type: none"> • spinal analgesia • sedation • respiratory depression • miosis • diuresis • dysphoria
sigma	σ	<ul style="list-style-type: none"> • dysphoria • hallucinations • respiratory and vasomotor stimulation • mydriasis
epsilon	ϵ	<ul style="list-style-type: none"> • stress response • acupuncture

Opioid Agonists and Antagonists

Endogenous Opioid Peptides

- first described by Hughes *et al.* in 1975
- three distinct families of peptides have since been identified,
 1. the **enkephalins** → met-ENK & leu-ENK
 2. the **endorphins** → β -END, α -END & γ -END
 3. the **dynorphins** → DYN-A, DYN-B, α -neodynorphin & β -neodynorphin
- each of these families is synthesised from a genetically distinct precursor polypeptide, which has a characteristic distribution within the body
- these are designated,
 - a. proenkephalin or proenkephalin-A
 - b. pro-opiomelanocortin POMC
 - c. prodynorphin or proenkephalin-B
- each of these contains a number of polypeptides, (see G&G fig. 22-1)
- POMC is cleaved to ACTH and β -lipotropin (LPH)
- β -LPH has no opioid activity but is cleaved to β -endorphin
- in spite of their differences, all of the three families of endogenous opioids possess the common amino-acid sequence,

Tyr - Gly - Gly - Phe

- the highest concentrations of ***b-endorphin*** occur in the pituitary gland and in the basal, medial, and arcuate regions of the hypothalamus
- there are some long axoned neurons which synapse in the septum, periaqueductal grey and thalamic regions of the midbrain
- it is unclear whether β -endorphin exists functionally in the spinal cord
- it does exist outside the CNS, in the placenta, small intestine, and in the plasma
- by contrast, the ***enkephalins*** are widely distributed throughout the CNS,
 - a. limbic system (amygdaloid & septal nuclei)
 - b. medial thalamic nuclei
 - c. periaqueductal grey matter & midline reticular formation in the midbrain
 - d. the periventricular grey areas in the medulla
 - e. laminae I, II & IV of the spinal cord (substantia gelatinosa)
 - f. the area postrema (CTZ)
- NB:** all of which are involved in the reception of ***afferent nociceptive*** information
- ***dynorphin*** is found in the hypothalamoneurohypophyseal axis but its function here is unclear
- it also is found in areas relevant to nociception, the limbic system, periaqueductal grey, thalamus, and laminae I & V of the dorsal horns

Opioid Agonists and Antagonists

Mechanisms and Sites of Opioid-Induced Analgesia

- opioids do not alter the threshold or responsiveness of afferent nerve endings, or the transmission along peripheral nerve fibres
- they may decrease conduction within primary afferent fibres entering the spinal cord
- opioid binding sites (**μ -receptors**) are located on the terminal axons of primary afferents within laminae I & II (substantia gelatinosa) of the spinal cord, and in the spinal nucleus of the trigeminal nerve
- here they decrease the **presynaptic** release of neurotransmitters, predominantly **substance P**
- **enkephalinergic** interneurons in the dorsal horn are predominantly inhibitory to the soma of cells in the deeper laminae IV & V
- morphine is **inactive** at these sites, at which met-ENK, a δ -receptor agonist inhibits neuronal firing

NB: in the spinal cord both **μ & δ receptors** are responsible for the inhibition of pain

- stimulation of pain fibres activates enkephalinergic neurones in the spinal cord, which play a role in the "gating" of pain and in mediating the effect of **descending medullary analgesic pathways**
- further modulation of nociception involves the periventricular and periaqueductal grey matter
- direct microinjections of morphine, or electrical stimulation produce analgesia which can be blocked by naloxone
- stimulation at this level results in barrages of impulses travelling in descending pathways to the dorsal horns of the spinal cord
- from these areas pathways bridge the medullary nuclei to the hypothalamus, amygdala and cortex
- there is also a high concentration of receptors in,
 - a. the caudal spinal trigeminal nucleus
 - which receives input from the face and hands via branches of the 5th, 7th, 9th and 10th cranial nerves
 - b. the solitary nuclei
 - which receive visceral input from the 9th & 10th cranial nerves and the area postrema
- in man, the distribution of endogenous opioids does not parallel the distribution of opioid receptors, except for kappa receptors & dynorphin
- the main mechanism underlying opioid action is the stimulation of stereospecific receptors, on or near Na⁺-channels, which results in a **decreased sodium conductance** in active membranes
- in addition, they may result in,
 - a. a local anaesthetic action, which is not stereospecific
 - b. increased gK⁺ & gCa⁺⁺, with membrane hyperpolarization
 - c. an effect at GABA receptors
- there appear to be additional, non-opioid nociceptive modulatory systems in the CNS
- **serotonergic** pathways are involved in the modulation of opioid induced analgesia
- α -adrenergic agonists such as **clonidine** have additive/synergistic effects

Opioid Agonists and Antagonists

- **tolerance** appears to result from **uncoupling** of the usual drug-receptor effect
- this is likely achieved by,
 1. a decrease in the **number** of receptors
 2. a reduction of their **affinity** for a given agonist, and
 3. a subcellular **uncoupling** of the receptor and second messenger
- there is little **cross-tolerance** between different receptor groups
- the high affinity agonists, ie. those with the greatest receptor reserve, are least prone to produce tolerance
- differing receptor affinities also explains the disparity between the duration of clinical effect for some agents and their plasma clearances
- radioligand-receptor studies have shown a marked and widespread reduction in mu and delta receptor densities with **age**
- this is a specific effect, as similar studies show an increase in benzodiazepine receptors
- the **cardiovascular** system also possesses opioid receptors, being located in,
 - a. the heart
 - b. branches of the cardiac vagus & sympathetic nerves
 - c. the medullary cardio-regulatory centres
 - d. the adrenal medulla
- **Other CNS Effects**
 - EEG changes shift toward low frequency, high voltage patterns and may result in decreases in REM sleep
 - two of the most important **excitatory** effects include,
 - a. nausea & vomiting
 - b. miosis
 - N&V is due to direct stimulation of the CTZ in the **area postrema** of the medulla
 - this is also stimulated by apomorphine, a **dopaminergic** agonist
 - some relief from the N&V of morphine is afforded by the phenothiazines which possess a dominant dopamine-blocking action
 - N&V is relatively uncommon in recumbent patients but occurs in 15-40% of ambulatory patients
 - therefore there may be a **vestibular** component
 - **miosis** is caused by most mu & kappa receptor agonists due to stimulation of the Edinger-Westphal nucleus
 - **pinpoint pupils** being pathognomonic of opioid poisoning

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- they generally decrease the responsiveness of the hypothalamus, causing,
 - a. lowered body temperature
 - b. decreased release of GnRH → lowered FSH, LH, ACTH & β-END
 - c. increased GH & prolactin ?? decreased dopaminergic inhibition
 - d. possibly changes in ADH secretion (disputed)

■ **Muscle Rigidity**

- high doses may produce muscular rigidity, characterised by increasing muscle tone progressing to severe stiffness, particularly in the thoracic and abdominal muscles
- the influence of **dose** and **rate of injection** has not been formally examined, but there appears to be a higher incidence with large boluses and rapid infusions (RDM)
- the incidence is also higher in the **elderly** and with the concomitant use of N₂O
- the highest incidence appears to be with **alfentanyl**
- it may occasionally occur upon **emergence** from anaesthesia and very rarely several hours after the last dose
- the occurrence of delayed rigidity may related to delayed, or second plasma peaks of fentanyl
- there is one report in a **neonate** whose mother received fentanyl
- abnormal muscle movements, from extreme flexion to global tonic-clonic activity, may occur
- whether these movements related to subcortical seizure activity is unknown
- the effect is probably **central**, rigidity being blocked by neuromuscular paralysis and there being no associated rise in serum creatinine kinase, suggesting there is little muscle damage
- the effect may be due to action on opioid receptors, plus dopaminergic & GABA'ergic interneurons, in the substantia nigra and striatum
- recent evidence implicates the **nucleus raphe pontis** as an integral central site in opioid rigidity

Effects of Opioid Induced Muscle Rigidity	
Pulmonary	<ul style="list-style-type: none"> • decreased compliance • decreased FRC • decreased V_M • hypercarbia • hypoxaemia
Cardiovascular	<ul style="list-style-type: none"> • increased CVP & PAP • increased PVR
Other Effects	<ul style="list-style-type: none"> • increased ICP • increased MRO₂ • dislodgement of lines • raised plasma fentanyl levels

- pretreatment with, or the concomitant use of the **nondepolarising muscle relaxants** significantly reduces the severity and incidence
- the severity may be reduced by the use of the **benzodiazepines**, though, this is contested

Opioid Agonists and Antagonists

■ Cerebral Blood Flow

- the opioids generally produce a modest (~ 10-15%) **decrease** in CMRO₂ and ICP
- in contrast to the volatile agents they are cerebral vasoconstrictors
- this occurs even in the presence of nitrous oxide
- Guy Ludbrook thinks they uncouple CBF & CMRO₂
- **morphine** (1-3 mg/kg + 70% N₂O) causes insignificant changes in CBF and CMRO₂
- **fentanyl** (100 µg/kg + 70% N₂O) causes dose related **decreases** in,
 - a. CBF to a maximum of 50%
 - b. CMRO₂ to a maximum of 35%
- similar changes are observed with sufentanyl and alfentanyl
- all of these agents decrease **CSF formation** while not affecting reabsorption
- therefore, some recommend their use in neuroanaesthesia

NB: however, alfentanyl and sufentanyl may **increase** ICP in patients with brain tumours, whereas fentanyl does not !
the reason for this difference is unknown

■ Thermoregulation & Shivering

- the volatile agents decrease the thermoregulatory threshold by ~ 2.5 °C
- evidence is scanty but it appears that N₂O/fentanyl results in a similar decrease, to ~ 34.5 °C
- shivering is common during recovery but its occurrence in relation to anaesthesia is inconsistent and incompletely understood
- it does however result in an increased minute ventilation, MRO₂, and cardiac output, with a decrease in the mixed venous PvO₂
- **pethidine** is unique among the opioids, in that 25-50 mg/70 kg, effectively terminates or attenuates shivering in 70-80% of patients
- pethidine is also effective **epidurally** when shivering occurs after epidural administration of local anaesthetic

NB: morphine and fentanyl are **ineffective**

Opioid Agonists and Antagonists

OPIOID ANAESTHESIA

- there is still considerable debate as to whether opioids in their own right produce anaesthesia
- to date there is **no study** showing that opioids alone, without muscle relaxants or other supplementation, will reliably produce anaesthesia in humans
- most studies assess the reductions in volatile MAC in animal models, demonstrating a **ceiling effect** which is subanaesthetic
- the problems with these studies include,
 - a. the profile of action of the opioids varies considerably with **animal species**, thus extrapolation to humans is not readily achieved
 - b. as inhibition of **motor responses** occur at deeper levels of anaesthesia than unconsciousness, amnesia and analgesia, methods requiring motor responses, eg. tail clamp studies, underestimate effect
 - c. the volatile agents inhibit descending inhibitory pain pathways activated by the opioids, therefore may decrease the effectiveness of the opioids
- however, the presumed specific action of the opioids would not be expected to produce anaesthesia
- others have postulated that the analgesia produced at subanaesthetic concentrations and the unconsciousness produced at higher levels may be mediated by different processes
- this **dual mechanism** hypothesis requires that in addition to the receptor mediated effects, an opioid must be lipid soluble enough to act as a general anaesthetic
- supporting this, a **biphasic response** has been noted with both fentanyl and sufentanyl

Awareness Under General Anaesthesia

- following the introduction of ether, this only again became a problem with the introduction of the muscle relaxants and the concept of "balanced anaesthesia"
- the most practical definition of awareness, is "the spontaneous recall of events occurring under general anaesthesia"
- the key point is recall should be **spontaneous**
- many studies have shown the persistence of auditory evoked potentials under general anaesthesia and there have been many studies on word/picture recognition
- awareness has been reported with many anaesthetic techniques and whether the use of opioid anaesthesia is associated with an increased incidence is debated
- reported incidences vary from 1-25%, though, a level of ~ **1-2%** is generally considered accurate
- there are a number of factors which influence the likelihood of anaesthesia being produced with opioid alone,
 - a. age
 - b. pre-existing disease states
 - c. patient habit - smoking, alcohol
 - d. acute tolerance
- although **pain** does not often accompany awareness, a national inquiry in the UK revealed an incidence of pain in ~ **41%** of cases of awareness

Opioid Agonists and Antagonists

• **age** is a major factor, the percentage of patients rendered unconscious following a dose of fentanyl 30 µg/kg being,

- a. 18-39 yrs ~ 57 %
- b. 31-45 yrs ~ 77 %
- c. 46-60 yrs ~ 53 %
- d. > 60 yrs ~ 100 %

- the detection of awareness is clinically difficult and usually limited to the possibility with increased **autonomic activity** during light anaesthesia
- tearing, sweating, tachycardia, pupillary dilatation, salivation, eyelid or head motion, and increased spontaneous respiratory effort are considered signs of too light anaesthesia
- the addition of supplemental hypnotic/sedative drugs decreases the likelihood of awareness, however they do not guarantee this and they frequently prolong postoperative sedation and respiratory depression
- the addition of 0.3-0.6 MAC of a volatile agent will usually ensure amnesia but frequently compromises the cardiovascular stability sought by an opioid based technique

Cardiovascular System

■ Morphine

- morphine & related opioids produce minimal effects in normal supine subjects
- however they do produce,
 - a. peripheral vascular dilation
 - b. reduced peripheral resistance
 - c. depression of the baroreceptor reflexes
 - **postural hypotension** in erect subjects
- these effects are produced by a number of mechanisms,
 - a. release of histamine
 - b. a direct centrally mediated reduction in sympathetic tone - reversed by naloxone
 - c. a vagal induced bradycardia
 - d. direct and indirect (P_{aCO_2}) mediated vasodilatation
 - e. splanchnic sequestration of blood
- although hypotension, hypertension, bradycardia and numerous other problems have been reported following morphine administration, these appear **less frequent** with fentanyl
- administration of 1.0 mg/kg slowly over 5-10 minutes usually **does not** result in significant changes in supine patients

Opioid Agonists and Antagonists

- the effects of morphine on the myocardium are not significant in normal man
- in patients with IHD, morphine reduces myocardial VO_2 , LVED pressure & work, therefore, it is acceptable for cardiac surgery c.f. the inhalational agents
- in patients with aortic valvular disease CO & SV may actually be increased
- Vasko *et al.* have demonstrated a positive inotropic effect in dogs, which is dependent upon release of endogenous catecholamines
- **catecholamine release** has been shown to parallel histamine release in patients with cardiac disease
- this effect is less pronounced with fentanyl and alfentanil
- most of the opioids decrease the ratio of sympathetic / parasympathetic tone when administered as a bolus dose
- if not counteracted by the release of endogenous catecholamines, or the administration of agents which modify the autonomic response, they may result in profound **hypotension**
- patients dependent upon a high level of sympathetic tone, or on exogenous catecholamines, are extremely subject to hypotension
- caution should be used in patients with a reduced circulating blood volume, or especially **corpulmonale** where sudden death has resulted
- the concurrent use of phenothiazines may exacerbate morphine induced hypotension

- **hypertension** during cardiovascular surgery has also been a problem with all of the opioids, morphine included
- the postulated mechanisms include, light or inadequate anaesthesia, reflex mechanisms, activation of the renin-angiotensin system, and sympathoadrenal activation

- with the exception of pethidine, **all** μ -receptor agonists are associated with **decreases** in HR
- factors associated with an increased risk of **bradycardia**, or asystole on anaesthetic induction with opioids,
 - a. treatment with Ca^{++} -channel, or β -adrenergic blockers
 - b. concomitant use of benzodiazepines
 - c. muscle relaxants with minimal vagolytic properties - vecuronium
 - d. muscle relaxants with vagotonic properties - succinylcholine
 - e. added vagal stimuli - laryngoscopy
 - f. rapid administration of the opioid

Opioid Agonists and Antagonists

■ Fentanyl

- fentanyl in analgesic (2-10 µg/kg), or anaesthetic (30-100 µg/kg) doses seldom causes significant decreases in blood pressure when given alone, even in patients with poor LV function
 - this may be due to its lack of effect on plasma histamine levels
 - virtually all CVS parameters remain significantly **unchanged** after anaesthetic doses of fentanyl
 - this is even less than that seen with sufentanyl or alfentanyl, thus fentanyl may be the choice of agent in patients with poor LV function
 - in contrast, most data suggests that alfentanyl is associated with more hypotension, bradycardia and surgically induced hypertension, than either fentanyl or sufentanyl
 - hypotension following fentanyl is mostly due to **bradycardia** and can be prevented by the use of anticholinergics, sympathomimetics or agents such as pancuronium
 - this is more likely to occur in patients with high pre-existing sympathetic tone
 - animal studies with effective autonomic paralysis confirm that the cardiac effect are almost certainly **indirect**
-
- **hypertension** is the commonest disturbance with high dose fentanyl anaesthesia, usually accompanying intubation, sternotomy, or aortic root dissection
 - this may be managed by increasing the dosage, however, this may result in unduly prolonged respiratory depression
 - the total dose is often limited to **£100 µg/kg** and haemodynamic control achieved by the use of,
 - a. supplemental volatile agent
 - b. supplemental intravenous agent
 - c. vasodilator therapy

■ Sufentanyl

- is ~ 5-10x as potent as fentanyl and causes **hypotension** with equal or greater frequency
- as it is presented in the same concentration as fentanyl, there is greater propensity for overdosage
- it does not increase the plasma histamine level but does induce a vagally mediated **bradycardia**
- as for fentanyl, the CVS effects are **centrally mediated**
- there is a greater degree of myocardial depression and hypotension, however, this is associated with a better attenuated response to intubation
- a number of studies suggest that sufentanyl is a more "complete" anaesthetic cf. fentanyl, and there is less need to use supplemental agents

■ Alfentanyl

- alfentanyl is an extremely short acting agent, which is ~ 1/5 to 1/3 as potent as fentanyl
- moderate doses result in minimal cardiovascular change and it shares most of the cardiovascular properties of fentanyl and sufentanyl at comparable doses
- very large doses (5 mg/kg) are associated with increases in HR, CO, PVR, and SVR
- other studies have found transient increases with moderate doses (200 µg/kg)
- it is the **least reliable** in blocking hypertensive responses during surgery
- thus it is unlikely to replace fentanyl or sufentanyl in cardiac anaesthesia

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Myocardial Ischaemia & Coronary Blood Flow

- the opioids **do not** protect against coronary ischaemia in animal models
 - whereas some protection may be offered by the volatile agents
 - also, the opioids are less effective in blunting the hypertensive responses during surgery
 - other studies have found that the opioids maintain the MRO_2/CBF ratio, as well or better than the volatile agents
 - **alfentanyl** has been associated with a **higher** incidence of myocardial **ischaemia**, as indicated by reversal of the coronary **lactate** gradient and decreases the the LVED compliance
 - frequently haemodynamic parameters are stable and **do not** reliably indicate ischaemia
 - Slogoff *et al.* compared sufentanyl versus the halothane, enflurane and isoflurane for CABG surgery and found no difference in,
 - a. perioperative myocardial ischaemia
 - b. postoperative MI, or
 - c. death
 - this occurred despite,
 - a. volatile induced hypotension was double sufentanyl
 - b. sufentanyl hypertension was double that of the volatiles
- NB:** **tachycardia** was the only variable significantly associated with ischaemia and it occurred with equal frequency in all groups
- the opioids have no significant effect on coronary vasomotion and do not interfere with **autoregulation** or the coronary response to drugs
 - this significantly contrasts the volatile agents which are coronary vasodilators

Opioid Supplements

- the rationale for the use of adjuvants to the opioids is,
 - a. reduce the incidence of **awareness**
 - b. control **hypertension**
 - c. decrease subsequent **respiratory depression**
- **nitrous oxide** is the most common supplement to high dose opioid anaesthesia
- alone it has minimal cardiovascular effects, mildly depressing cardiac contractility in humans
- however, in association with the opioids, N_2O results in significant **cardiovascular depression**
- these changes occur with all of the opioids in virtually all studies
- a lower F_1O_2 may be in part responsible
- myocardial ischaemia may occur and increases in systemic vascular resistance may contribute to the reduction in cardiac output
- this later aspect may mask myocardial depression by maintaining arterial pressure

Opioid Agonists and Antagonists

- **inhalational agents** similarly depress the myocardium, however, tend to do so in a more predictable and dose dependent fashion
 - their addition allows a continued high $F_{I}O_2$ and will control haemodynamic responses when opioids alone are insufficient
 - low concentrations of **isoflurane** have been used successfully during sufentanyl anaesthesia
 - however, undesirable cardiovascular depression can occur during supplementation with these agents, especially halothane
 - an undesirable **redistribution** of coronary blood flow may occur with both isoflurane and enflurane
 - even so, the ease of addition and titration of these agents makes them useful adjuvants
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- **benzodiazepines** produce minimal cardiovascular disturbance when administered alone
 - this, plus their **amnesic** qualities make them a desirable supplement to the opioids
 - they are synergistic and decrease the quantity of opioid required for "anaesthesia"
 - however, when combined with the opioids they frequently result in significant **cardiovascular depression**
 - some studies have suggested that lorazepam & fentanyl may produce less depression than other combinations
 - most studies indicate that benzodiazepines, even as premedication, cause significant reductions in CI, HR, BP, and SVR
 - the mechanism is probably centrally mediated
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- other adjuvants include,
 1. **b-blockers**
 - i. reduce opioid requirements and the need for supplements
 - ii. improve haemodynamic stability
 - iii. decrease the intra/postoperative incidence of myocardial ischaemia
 - iv. decrease the incidence of dysrhythmias
 2. **α_2 -agonists**
 - have been studied little to date
 - clonidine has been evaluated as a premedicant, where it,
 - i. reduces anaesthetic requirements ? decreasing SNS outflow & nociception
 - ii. allows earlier extubation
 - iii. lower plasma catecholamine levels
 - iv. less shivering
 - v. higher cardiac outputs
 - respiratory function is well preserved when morphine 0.2 mg/kg + clonidine 0.2-0.4 mg is administered as premedication
 3. **Ca^{++} -entry blockers (CEB)**
 - can significantly depress **contractility** when combined with the volatile agents
 - opioid / CEB interactions appear to be mild to moderate
 - the presence of other agents and state of LV function appear to be more important

Opioid Agonists and Antagonists

Respiratory System

- all **μ -receptor agonist** cause a dose dependent depression of respiration,
 1. reduction in the brainstem sensitivity to CO₂
 - decrease in the slope of the CO₂-ventilation response curve
 2. increase in the ***apnoeic threshold***
 3. decrease the ***hypoxic drive*** to respiration
 - carotid body chemoreception is virtually abolished by analgesia doses of opioids
 4. depression of pontine & medullary centres involved in rhythmic respiration

NB: they ***do not*** however affect hypoxic pulmonary vasoconstriction

- high concentrations of opioid receptors are located in the nucleus tractus solitarius, nucleus retroambigularis and nucleus ambiguus, all of which are intimately involved in respiratory regulation
- respiratory depression may be governed by a separate group of receptors, μ_2 c.f. the μ_1 -receptors involved in analgesia (G&G, RDM)
- initially the ***respiratory rate*** is affected more than tidal volume, but as the dose is increased all phases of respiration are depressed
- both natural sleep and the opioids relatively spare the diaphragmatic component of respiration, impairing predominantly ***thoracic excursion***
- even small analgesic doses markedly accentuate the normal right-shift of the CO₂-ventilation curve seen in normal sleep
- the cough reflex is also depressed by a central mechanism
- all of the respiratory effects are greater in the ***elderly*** (≥ 60 yrs)
- the immature BBB of ***neonates*** allows greater penetration of morphine, usually excluded due to its low lipid solubility
- this difference is not seen with the highly lipid soluble agents
- the respiratory depressant effects are potentiated by any other CNS depressant drugs, especially the volatile agents, alcohol, the benzodiazepines and barbiturates

NB: exceptions to this rule are ***scopolamine & droperidol***

- morphine is dangerous in patients with respiratory insufficiency and should be used cautiously in asthmatics as large doses may produce ***bronchospasm***
- fentanyl has antimuscarinic, antihistaminergic and antiserotonergic actions, and is therefore superior to morphine in asthmatic patients
- respiratory depression following ***fentanyl*** outlasts its analgesic effects $\sim 2x$ (60 vs. 20-30 min)
- studies have found respiratory depression up to 5 hrs after induction with fentanyl 10 $\mu\text{g}/\text{kg}$
- recovery from the ventilatory effects of fentanyl closely parallel ***blood levels***, cf. morphine where depression persists despite falling plasma levels
- with induction doses of fentanyl (50-100 $\mu\text{g}/\text{kg}$) depression may persist and require ventilatory support for 12-18 hours
- pharmacokinetic data predict and clinical studies have confirmed that both alfentanil and sufentanil allow more rapid recovery of respiratory function than fentanyl
- the respiratory pharmacodynamic effects of alfentanil and sufentanil are indistinguishable from those of fentanyl

Opioid Agonists and Antagonists

- *delayed respiratory depression* has been reported with most of the opioids, including morphine, pethidine, fentanyl, alfentanil, and sufentanil
- the exact cause of this phenomenon is unclear and may result from,
 - a. secondary plasma drug peaks
 - sequestration of ~ 20% of fentanyl in the stomach
 - large peripheral storage compartments (skeletal muscle)
 - b. supplemental analgesics and other medications
 - c. lack of nociceptive stimulation

Factors Increasing Opioid Respiratory Depression
Increasing dose
Intermittent bolus vs. continuous infusion
Increased brain penetration, or drug delivery <ul style="list-style-type: none">• decreased distribution, low CO• increased unionised fraction (respiratory alkalosis)
Decreased reuptake from the brain (respiratory alkalosis)
Decreased drug clearance <ul style="list-style-type: none">• decreased liver blood flow (abdominal surgery)• intrinsic liver disease
Secondary plasma drug peaks <ul style="list-style-type: none">• peripheral storage compartments, lung, fat, muscle• sequestration in the stomach
Increased ionised fraction at the receptor site (respiratory acidosis)
Sleep
Increasing age (≥ 60 yrs) and neonates
Metabolic alkalosis

Opioid Agonists and Antagonists

Gastrointestinal Tract

- the use of opium for the relief of *diarrhoea* preceded its use for analgesia by many centuries
- the effects seen in man (species differ markedly) include,
 - a. some decreased HCl secretion
 - b. decreased gastric motility & increased antral tone
 - c. decreased tone of the lower oesophageal sphincter
 - d. increased tone in the 1st part of the duodenum
 - delayed *gastric emptying* & delayed *drug absorption*
 - e. biliary & pancreatic secretions are decreased
 - f. increased resting tone & periodic spasms of the SI
 - g. increased amplitude of *non-propulsive* contractions
 - h. propulsive contractions are markedly decreased, especially proximal⁺⁺
 - i. water reabsorption is increased ≡ increased transit time
 - j. viscosity of chyme is increased ≡ water reabsorption
 - k. increased tone of the ileo-cecal valve
 - l. propulsive contractions of the LI are diminished ± abolished
 - m. resting tone in the LI is increased to the point of spasm
- these effects are mediated by central (vagal) and peripheral (myenteric opioid and cholinergic receptor) mechanisms
- even in small doses, opioids decrease the release of ACh from *presynaptic* terminals in the GIT
- thus, large doses of *atropine* may partly reverse the effects of morphine
- resection of the extrinsic nerve supply or ganglionic blockade do not do so
- *all* opioids cause a dose related increase in tone of the *sphincter of Oddi* and a marked increase in biliary tract pressure ($\leq 10x$)
- the duration of this effect is closely parallels plasma opioid levels
- this may cause a marked exacerbation of biliary colic, or result in severe *epigastric pain* which may be confused with biliary or cardiac disease
- most studies suggest the mixed agonist-antagonist agents produce less of an effect
- the increases in biliary pressure are, with the exception of that caused by pethidine, reversed by *naloxone*
- *glucagon*, 1-3 mg carefully titrated may also relieve opioid induced biliary spasm
- fentanyl increases intestinal blood flow, and decreases MRO_2 , in a dose dependent manner
- thus it may increase mesenteric portal PvO_2 and hepatic oxygenation
- the opioids result in mild decrease in liver function, similar to that caused by the volatile agents

Opioid Agonists and Antagonists

Genitourinary System

- morphine has significant ADH properties, which may be due to CNS release
- release of ADH only occurs under unusual circumstances, eg. vomiting or surgical stimulation in lightly anaesthetised patients
- antidiuresis after morphine administration has been attributed to decreases in RBF and GFR
- studies comparing postoperative urine function in volatile versus high dose opioid anaesthesia show no significant difference, unless the dose of morphine is sufficient to decrease mean arterial pressure
- ***kappa agonists*** result in a free water diuresis by either decreasing the secretion of ADH, or altering the distal tubular response
- most available data suggests these effect for fentanyl, alfentanyl, and sufentanyl are clinically insignificant
- ureteric tone and peristalsis are increased
- tone of the detrusor muscle is increased, as is the tone of the internal urethral sphincter
 - urinary retention & urgency
- large doses may prolong labour and restore normal tone in an oxytocic excited uterus, however the mechanism is unclear

Endocrine System Effects

Def'n: "***stress response***" the overall normal metabolic response to surgery, characterised by hypermetabolism and mobilisation of energy stores

- plasma concentrations of most stress hormones increase with general anaesthesia and are increased further with surgical stimulation
- these increases are presumed to be undesirable as they promote cardiovascular instability intraoperatively and in the postoperative period
- the exact nature of these responses depends upon a number of factors, including,
 - a. afferent nerve function from the affected area
 - b. pain
 - c. hypovolaemia and haemorrhage
 - d. arterial pH, hypoxia, temperature changes
 - e. CNS injury
 - f. starvation
 - g. drugs
 - h. immune status

Opioid Agonists and Antagonists

• despite the variability of the stimulus, the body has a number of common responses to an insult, these include,

- a. pituitary trophic hormones - ACTH, GH, ADH
- prolactin, endorphin
- b. catabolic hormones - cortisol, catecholamines
- thyroxine
- glucagon

NB: in addition, plasma levels of the *anabolic hormones*, insulin and testosterone, are usually *decreased*

- the opioids are effective in reducing these responses, however, the precise mechanism is unclear
- they are capable of reducing nociceptive input and altering neuroendocrine responses
- there are a number of different hypothalamic opioid receptors and the *endogenous opioids* appear to act themselves as stress hormones
- the greatest evidence for this is the cosynthesis of *b-endorphin* and ACTH within POMC
- while morphine inhibits the pituitary-adrenal response to stress, it increases some of the stress related hormones
- levels of plasma *catecholamines* increase, probably due to,
 - a. histamine release
 - b. direct adrenal release
 - c. release from sympathetic nerve endings

- *fentanyl* and its congeners appear to be more effective than morphine in modifying the stress response
- fentanyl is more effective than halothane in abolishing the rise in cortisol and GH seen with surgery
- except during *CABG surgery*, fentanyl more effectively attenuates the rise in plasma catecholamines
- sufentanyl and alfentanyl are possibly more effective during CABG procedures
- although the fentanyl series appear more effective in abolishing the endocrine response to surgery, the clinical importance of this difference is still unproven
- with the administration morphine, there is *no* improvement in postoperative nitrogen balance

Tolerance and Opioid Abuse

- addicted patients have a number of problems important to anaesthesia
- these include,
 1. bacterial endocarditis - especially tricuspid
 2. septic pulmonary and systemic embolization
 3. systemic sepsis
 4. thrombophlebitis
 5. mycotic aneurysm
 6. cardiac tamponade and dysrhythmias
 7. pulmonary oedema
 8. pulmonary aspiration and abscesses
 9. pulmonary hypertension
 10. talc granulomata
 11. nephrotic renal disease
- **restrictive lung disease** and an increased P_{A-aO_2} gradient are particularly common
- chronic morphine administration causes adrenal hypertrophy and impaired cortisol secretion
- other problems which occur with increased frequency in addicted patients include,
 1. viral and non-viral hepatitis
 2. HIV infection
 3. osteomyelitis
 4. muscle weakness associated with rhabdomyolysis and myoglobinuria
 5. neurological complications
 - transverse myelitis
 - encephalitis
 - cerebral abscesses
- routine management of these patients should **not** involve the avoidance of opioids, and these should be used on an as required basis, as for any patient
- patients with an acute overdose are frequently hypotensive, bradycardic, hypothermic, apnoeic or hypoventilating, and have a full stomach due to decreased motility

Opioid Agonists and Antagonists

Allergic and Adverse Effects

- true allergic reactions to the opioids are *rare*
- most patient claiming to be "allergic" to opioids have simply suffered adverse effects, eg. pruritis
- fentanyl and pethidine have both been associated with *anaphylactoid reactions*
- local reactions are thought to be due to local release of histamine, or result from additives
- ampoules of fentanyl do not contain preservatives, however vials do

- *pethidine* is unique, in that co-administration with *monoamine oxidase inhibitors* may result in the *malignant neurolept syndrome*, resulting in,
 - a. hyperthermia
 - b. labile arterial BP
 - c. respiratory depression
 - d. convulsions and coma

- thus, in patients on MOA inhibitors, fentanyl or morphine are safer choices
- fentanyl, alfentanyl and sufentanyl are *not teratogenic*
- older studies implicated the older opioids, however, the results were compromised by concomitant respiratory depression
- the fentanyl series cause no alteration of uterine blood flow, uterine tone or maternal/foetal acid-base balance

Opioid Agonists and Antagonists

MORPHINE

Central Nervous System

- the primary actions of morphine on the CNS are,
 - i. analgesia
 - ii. reduced levels of consciousness
 - iii. changes in mood
 - iv. mental clouding
- a significant feature of the analgesia is that it occurs without loss of consciousness
- some patients may also experience *euphoria*
- given to pain-free subjects, morphine may lead to *dysphoria*, with increased fear and anxiety
- *nausea & vomiting* may also occur and these are due to excitatory effects
- the balance between excitation and depression depends markedly on the species
- in man, depressive effects predominate and analgesia is said to be due to,
 - i. altered perception
 - ii. euphoria and sedation
 - iii. elevation of the pain threshold
- clinically, morphine is more effective in relieving constant, dull pain than sharp, intermittent pain
- the relief of pain by morphine is relatively selective, in that other sensory modalities are preserved, ie. touch, vibration, vision, hearing etc.
- this selectivity of morphine is greater than many other drugs that act on the CNS,
 - a. N₂O
 - at 20 to 40%, analgesia is \equiv 15mg morphine, but produces a marked impairment of consciousness, mental functioning, immediate & delayed memory
 - b. ether & alcohol
 - marked sedation
 - impaired motor coordination, intellectual acuity, emotional stability, and judgment
- for a given degree of analgesia, the mental clouding produced by morphine is much *less* than other agents and qualitatively different
- morphine rarely produces the garrulous, silly & emotionally labile behaviour seen with alcohol or the barbiturates
- opioids obtund the response to pain at several loci within the CNS
- not only is the sensation of pain diminished, but the affective response is also altered
- intrathecal administration of morphine can result in profound segmental analgesia, without significant alteration of motor or sensory function
- termed by Cousins as "*selective spinal analgesia*"
- morphine raises the ICP, due to P_{aCO₂} induced vasodilation, subsequent to depression of the CNS response to hypercapnia

Opioid Agonists and Antagonists

Pharmacokinetics

■ Absorption & Distribution

- the absorption of morphine after oral administration has long been stated to be poor and unpredictable
- this, together with the high hepatic *extraction ratio* ~ 0.7, has steered usage away from the oral route
- more recent studies have shown the *oral bioavailability* to be only moderate but reasonable reproducible ~ 15-49% (G&G)
- following IV administration, morphine rapidly leaves the blood stream
- the distribution half life, $t_{d/2}$ ~ 1.65 min, the drug rapidly entering the parenchymal tissues of the liver, lung, spleen, kidney, adrenal & thyroid
- however, only small amounts enter the *brain*
- a relatively lesser amount enters skeletal muscle, however due to its large mass this accounts for the major fraction of morphine in the body
- serum concentrations are low, reflecting the high V_{dss} ~ 3.2 l/kg
- plasma *protein binding* ~ 33%
- only small amounts cross the BBB, however significant amounts cross the placenta and result in neonatal respiratory depression
- the elimination half-life, $t_{b/2}$ ~ 180 min

■ Biotransformation & Excretion

- less than 10% is excreted unchanged in the urine in the first 24 hrs
- the major pathway for elimination is conjugation in the liver with glucuronic acid
 - the urine and bile as *morphine-3-glucuronide*
- N-demethylation does occur but this is a minor pathway
- the average adult plasma half-life ~ 2.5-3 hrs, may be slightly shorter in young patients and longer in the elderly
- over 90% of the administered dose is excreted in the first 24 hrs
- however traces of both free & conjugated morphine are found in the urine ≤ 48 hrs
- only a small fraction, ~ 7%, is excreted in the feces

Opioid Agonists and Antagonists

Variations in Response, Adverse Reactions & Precautions

- morphine and its related opioids produce a number of unwanted *side-effects*,

- a. nausea & vomiting
- b. mental clouding, drowsiness, dysphoria
- c. raised biliary tract pressure

NB: these occur *commonly*, though, many patients do not experience such effects

- allergic phenomena to the opioids do occur, though, these are *rare* and usually only mild
- anaphylaxis has been reported, ? sudden death in addicts
- a number of factors alter individual sensitivity to the opioids, including the integrity of the BBB, morphine administered to the mother prior to delivery may cause severe respiratory depression in the newborn
- other opioids are not as dependent upon the BBB for entry to the CNS and are relatively less selective for the neonate, e.g. pethidine
- conditions in which morphine should be used with caution,
 - a. reduced circulating blood volume
 - b. decreased respiratory reserve - obesity
 - kyphoscoliosis
 - emphysema
 - obstructive airways disease (*cor pulmonale)
 - asthma
 - c. hypothyroidism
 - d. multiple sclerosis
 - e. head injuries with the possibility of raised ICP
 - f. prostatic hypertrophy

■ Interactions With Other Drugs

- the depressant effects of some of the opioids may be exaggerated, or prolonged by,
 - a. phenothiazines
 - b. tricyclic antidepressants
 - c. MAO inhibitors
- the mechanisms for these interactions are poorly understood, however for some of these drugs there appears to be receptor/transmitter interactions
- obviously, any other direct CNS depressant is contraindicated in the presence of morphine

Opioid Agonists and Antagonists

CODEINE

- classified as a simple, or mild analgesic, codeine is often used in low doses as an oral analgesic
- produces antitussive and constipating effects at doses below those required for significant analgesia
- given s.c., 120 mg of codeine is equi-analgesic to 10 mg of morphine, however there is no advantage of the former
- unlike morphine, has a higher oral / parenteral potency ratio ~ 2/3
- ~ 10% of the administered dose is demethylated to morphine
- orally, 30 mg of codeine is equi-analgesic to 600 mg of aspirin, however, the effects of the two are additive, and occasionally synergistic

HYDROMORPHONE

- 2 mg hydromorphone ~ 10 mg morphine
- but the drug is more effective than morphine when given *orally*
- available in tablets, rectal suppositories, & solutions

OXYCODONE

- actions and potency similar to morphine, however, like codeine it is ~ 1/2 as effective orally as parenterally
- available as 5 mg tablets, solution and in combination with other analgesics
- average dose ~ 5-10 mg q6h

APOMORPHINE

- is a *dopaminergic agonist*, used for its action on the CTZ to induce emesis
- it has minimal analgesic properties
- obtained by the exposure of morphine to strong mineral acids

PETHIDINE

- is a *phenylpiperidine* derivative, introduced by Eisleb & Schaumann in 1939, originally studied as one of a number of *atropine-like* agents
- there are a number of closely related congeners,
 - i. alphaprodine
 - ii. diphenoxylate (+ atropine = LOMOTIL)
 - iii. fentanyl
 - iv. alfentanyl
 - v. sufentanyl
 - vi. lofentanyl
- there are two main uses of pethidine,
 1. premedication prior to anaesthesia
 2. analgesia in acute, or chronic pain

Central Nervous System

- produces a pattern of effects similar, but not identical, to morphine
- pethidine, and/or its metabolites, may be more potent at *k₂-receptors*
- onset of analgesia (s.c./i.m.) is ~ 10 min, however the duration, 2-4 hrs is slightly shorter than morphine, therefore more frequent administration is required
- quantitatively, 80-100 mg pethidine ~ 10 mg of morphine
- at these doses, the analgesic, sedative and euphoric effects of the two agents are almost identical
- produces corneal analgesia and hence abolishes *corneal reflexes*
- stimulates the CTZ and the labyrinthine apparatus → N,V & dizziness
- EEG changes are similar to morphine, however they may persist for several days due to the presence of *norpethidine*
- prolonged administration of large quantities may result in accumulation of norpethidine & CNS convulsions
- usually doses > 1000 mg/day for several days (adult), but has been reported at lower doses

Respiratory System

- at equipotent analgesic doses respiratory depression is similar, however, respiratory rate is less effected less & tidal volume more
- peak depression occurs ~ 1 hr after i.m. injection and tends to return to normal by 2 hours
- these effects are antagonised by naloxone

Opioid Agonists and Antagonists

Cardiovascular System

- in usual doses, has no significant untoward effect on the CVS
- there is a small increase in peripheral blood flow due to a decrease in arteriolar and venous tone, though, unlike morphine there is **no** histamine release
- myocardial contractility is not depressed and the ECG unaltered
- due to increased P_{aCO_2} due to respiratory depression, cerebral vasodilation and raised ICP are similar to morphine

Smooth Muscle

- like morphine, pethidine has a spasmogenic effect on certain smooth muscles, however the intensity is much **less** relative to its analgesic action
- thus, pethidine is the agent of choice for renal or biliary colic
- gastric emptying is markedly reduced, altering the kinetics of orally administered drugs, e.g. paracetamol in pregnant mothers
- these effects are **not reversed** by metoclopramide
- therefore, the administration of opioids in obstetric practice, where emergency anaesthesia may be required, increases the risk of Mendelson's syndrome
- the uterus is mildly stimulated by pethidine, however the effects are clinically insignificant
- pethidine does not cause as much constipation as morphine and this may relate to its shorter duration of action

Pharmacokinetics

- pethidine may be administered orally, s.c., or i.m.
- variable oral **bioavailability** ~ 45-75%, reaching peak plasma concentrations at ~ 2 hrs
- plasma concentrations after i.m. injections show marked variation, especially in surgical patients, though, maximum levels are normally achieved by ~ 20 mins
- following i.v. injection, elimination is multiphasic, with rapid and extensive extravascular distribution which is essentially complete in 30-45 minutes, and a terminal half-life, $t_{1/2\beta}$ ~ 3 hrs (some report ~ 8 hrs)
- plasma **protein binding** ~ 60%
- plasma clearance is high ~ 700-1300 ml/min and less than 5% of the administered dose is excreted unchanged
- pethidine is metabolised in the liver,
 - a. **N-demethylation** ~ 1/3 → norpethidine
 - b. **hydrolysis** pethidine → pethidinic acid
norpethidine → norpethidinic acid
 - c. **conjugation** of both acid products
- **norpethidine** ~ 50% analgesic activity, however its convulsant activity is ~ 2x that of pethidine

Opioid Agonists and Antagonists

- urinary excretion of pethidine is pH dependent, up to 25% of the drug may be excreted unchanged in the urine if it is highly **acidified**, however this does not significantly affect plasma levels
- **renal failure** may cause accumulation of the active metabolites of pethidine
- in patients with **cirrhosis** the bioavailability is increased, the plasma clearance decreased and the half lives of both pethidine and norpethidine are prolonged
- **elderly** patients have higher serum concentrations for a given dose compared to young adults
- possibly due to decreased protein binding, plasma clearance and V_{dSS} , therefore they should receive lower doses

Pregnancy & Neonatal Considerations

- commonly used for pain relief during labour
- pethidine crosses the placenta readily and can result in neonatal respiratory depression
- umbilical cord:maternal blood ratios vary between 0.8-1.0:1.0
- metabolites may be responsible for some of the neonatal depression, however, cord norpethidine concentrations are generally low
- the neonatal clearance of pethidine is markedly lower than the adult and highly dependent upon urine flow
- **neonates** may take up to 6 days to completely eliminate the drug, $t_{b\frac{1}{2}} \sim 24$ hrs

Dosage & Adverse Effects

- recommended adult dose is 75-100 mg i.m., repeated 3 hrly as required
- adverse effects (essentially = morphine),
 - a. respiratory depression
 - b. nausea & vomiting
 - c. drowsiness, dysphoria, impaired cerebation
 - d. syncope

NB: may produce a severe drug interaction with the **MAO inhibitors**, possibly due to potentiation of pethidine biotransformation in the liver,

→ excitation, convulsions, hyperpyrexia, hypotension, and respiratory depression

- pethidine causes constipation far less than morphine
- large doses produce muscle tremors, dilated pupils, hyperactive reflexes and convulsions

Opioid Agonists and Antagonists

FENTANYL

- a synthetic opioid, related to the phenylpiperidines, with a *potency ~ 80x morphine*
- like morphine fentanyl is primarily μ -receptor agonists
- in equianalgesic doses they produces about the same degree of respiratory depression, however, this is of shorter duration than pethidine or morphine
- ?? the sedative and hypnotic activity is less than the other two agents
(G&G doesn't agree with this last statement from W&W)
- there have been reports of postoperative respiratory depression after fentanyl, despite its short duration of action
- fentanyl is noted for its rapid onset and short duration of action
- the euphoric and hypnotic effects are antagonised by naloxone, however are relatively unaffected by *droperidol*, with which it is commonly used to provide neurolept analgesia
- provided respiration is maintained, even with very large doses cardiovascular stability is preserved
- at high doses, fentanyl may increase the *rigidity* of respiratory muscles, decreasing compliance
- the main uses of fentanyl are,
 - a. balanced anaesthesia + O₂ / N₂O / volatile
 - b. neurolept analgesia + droperidol
 - c. "cardiac" anaesthesia + O₂ \pm volatile or other supplement
- droperidol acts as an α -blocker and vasodilation is common with the later practice
- however, CVS stability is good and any hypotension is easily treated with appropriate fluid replacement
- occasionally used in high-dose anaesthesia due to CVS stability and the reduced catabolic response to trauma, however, respiratory depression is common and reversal with naloxone may lead to agitation and a withdrawal-like syndrome
- the usual adult dose is 100-200 μ g and up to 600 μ g may be given if respiration is controlled

Pharmacokinetics

- usually described by a 3 compartmental model
- > 98% of the administered dose is removed from the plasma within the first hour
- brain levels parallel those in blood, with distribution constants,
 - i. $t_{1/2\alpha 1}$ ~ 1-2 minutes
 - ii. $t_{1/2\alpha 2}$ ~ 10-30 minutes
 - iii. $t_{1/2\beta}$ ~ 2-4 hours
- spectral edge studies suggest administration is best ~ *5 minutes* prior to known noxious stimuli
- alternatively, a large bolus may be administered to saturate both brain receptors and non-receptor storage sites

Opioid Agonists and Antagonists

- animal studies show > 50% of the administered dose may be held in *muscle* & ~ 20% in fat
- the high lipid solubility and high V_{dss} limit hepatic access to the drug and contribute to the wide variation in plasma levels during the distribution phase
- the high clearance and hepatic ER minimise *enterohepatic circulation* of fentanyl
- however, decreases in hepatic blood flow decrease elimination of fentanyl
- primarily metabolised by N-dealkylation, the activity of metabolites being unknown
- the high pKa ~ 8.4, results in > 90% being in the ionised form
- plasma *protein binding* ~ 40%
- the terminal half life may be prolonged with either very large, or repeated administration and this may be responsible for the occasional case of postoperative respiratory depression

Relative Potencies		
Agent	Relative Potency	Anaesthetic Dose
Morphine	1	~ 1-3 mg/kg
Alfentanyl	20	~ 50-200 µg/kg
Fentanyl	80	~ 50-100 µg/kg
Sufentanyl	800	~ 2-20 µg/kg
Lofentanyl	6,000	research

Opioid Agonists and Antagonists

Pharmacokinetic Data					
Agent	Morphine	Pethidine	Fentanyl	Alfentanyl	Sufentanyl
pKa'	8	8.5	8.4	6.5	8
% Unionized	23%	< 10%	< 10%	90%	20%
$\tau_{\text{Octanol:H}_2\text{O}}$	1.4	39	813	145	1778
$t_{1/2\alpha 1}$ (min)	1.0-2.5		1-2	1-3	1-2
$t_{1/2\alpha 2}$ (min)	10-20	5-15	10-30	4-17	15-20
$t_{1/2\beta}$ (hrs)	2-4	3-5	2-4	1-2	2-3
V_{dSS} (l/kg)	3-5	3-5	3-5	0.4-1.0	2.5-3.0
Cl (ml/kg/m)	15-30	8-18	10-20	4-9	10-15
ER	0.8-1.0	0.7-0.9	0.8-1.0	0.3-0.5	0.7-0.9

OPIOIDS WITH MIXED ACTIONS

- agents in this group bind to the μ -receptors, therefore can compete with other agents, however, they either exert no effect, *competitive antagonists*, or only a limited effect, *partial agonists*
- drugs such as nalorphine, cyclazocine and nalbuphine are competitive antagonists at μ -receptors, thereby antagonize the effects of morphine
- however, these agents act as *partial agonists* at other receptors, κ & σ
- pentazocine qualitatively resembles these three agents, but is a much weaker antagonist at μ -receptors and stronger agonist at κ -receptors
- propriam and buprenorphine have partial agonist actions at μ -receptors

PENTAZOCINE

- pentazocine was synthesised as a part of a deliberate effort to develop an effective analgesic without the potential for abuse
- this latter hope is not the case, though, considerably less so than morphine
- is a *benzomorphan* of similar potency to morphine and in the N-allyl derivative of phenazocine
- it has both agonist actions and weak antagonist actions
- the large allyl substituent, on what would be the N₁₇ position of morphine, is a common structural feature of a number of the opioids with mixed agonist/antagonist actions (see G&G 7th Ed., p520)
- the analgesic and respiratory depressant actions of the racemate are largely due to the *l-isomer*
- a dose ~ 20-30 mg is equipotent to 100 mg of pethidine, or 10 mg of morphine

■ Central Nervous System

- the pattern of CNS effects produced by this drug are generally similar to those of morphine, including analgesia, sedation and respiratory depression
- however, pentazocine resembles cyclazocine & nalorphine in that it produces a type of analgesia which differs from that of morphine, the *euphoria* and sense of well being are *absent*
 - pentazocine clearly interrupts nociceptive input in the *spinal cord*, while morphine also acts at supraspinal sites in producing analgesia
- thus, it is probable that the analgesic effects of pentazocine are mediated by actions primarily at *k-receptors*
- increasing the dose > 60-90 mg results in nalorphine-like *dysphoric* and psychotomimetic effects, these can be antagonised by naloxone but not nalorphine and are probably due to actions at *S-receptors*
- pentazocine acts as a weak antagonist at μ -receptors, being only ~ 1/50th as potent as nalorphine
- it *does not* antagonise the respiratory depression produced by morphine, however when given to addicts may precipitate withdrawal symptoms

Opioid Agonists and Antagonists

■ Respiratory System

- pentazocine produces a similar degree of respiratory depression to morphine at equi-analgesic doses, however, increasing the dosage above 30 mg does not produce a proportionate increase in respiratory depression
- studies indicate that a **ceiling effect** is reached at ~ 60 mg in a 70 kg man
- the respiratory effects can be reversed by naloxone

■ Cardiovascular System

- differs from morphine as **does not** produce hypotension or bradycardia
- actually produces a slight rise in HR & BP, suggesting that it may increase the MRO_2
- in patients with MI, pentazocine has been shown to elevate the LVED pressure and should therefore be **avoided** in subjects with **IHD**
- plasma catecholamines are increased and these may account for these effects

■ GIT

- similar for the other opioids → delayed gastric emptying and reduced propulsive activity in the intestines

Pharmacokinetics

- may be administered by either the oral, i.m. or i.v. routes, though, there is considerable intersubject variation
- it is well absorbed from the GIT and other sites
- maximum serum concentrations are reached at 15-60 min after i.m. injection and at 1-3 hrs after oral administration
- plasma **half-life** ~ 2-3 hrs
- first pass metabolism is extensive and oral bioavailability ~ 20%
- elimination is largely via biotransformation in the liver
 - oxidation of the terminal methyl groups & glucuronidation, then excretion in the urine
- greater than 60% appears in the urine after the first 24 hrs
- there is considerable intersubject variability in the rate of biotransformation and this may account for the variation in analgesic response
- marketed as 50 mg tablets and as 30 mg/ml injectable solution

Opioid Agonists and Antagonists

■ Adverse Effects

- although pentazocine has a low abuse potential, it can produce both psychological and physical dependence
- tablets marketed in the USA with naloxone to remove possible source for IV use, naloxone is hydrolysed in the GIT
- because it is a weak antagonist at μ -receptors it may produce *withdrawal symptoms* in addicts
- as for morphine, the following are side-effects,
 - a. sedation, respiratory depression
 - b. dizziness, sweating and nausea - rarely vomiting
 - c. raise ICP
 - d. may cause nalorphine-like dysphoria at high doses
- care should be taken where there is reduced respiratory or liver reserve

BUTORPHANOL

- butorphanol is a morphinan congener with a profile of actions similar to pentazocine
- it is about 3.5-5 times as potent as morphine, average dose ~ 2-3 mg i.m.
- oral bioavailability is low, ~ 15-20%
- the onset, peak and duration of action are similar to morphine
- the plasma elimination half-life ~ 3 hrs
- respiratory depression exhibits a *ceiling effect* and can be reversed by naloxone
- like pentazocine it increases BP, LVEDP & PAP, therefore, should be avoided in IHD
- the incidence of psychotomimetic effects is lower, but qualitatively similar, to pentazocine
- undergoes extensive liver metabolism, mainly hydroxylation to hydroxybutorphanol but also to norbutorphanol (10%), followed by urinary excretion (70%)
- readily crosses the placenta and foetal levels may *exceed* maternal levels
- same precautions and recommendation c.f. pentazocine

Opioid Agonists and Antagonists

NALBUPHINE

- is structurally related to both oxymorphone and naloxone, and has a spectrum of activity similar to pentazocine and nalorphine
- however, nalbuphine is more potent an antagonist at μ -receptors than either of these agents
- hence is less likely to produce the dysphoric, or psychotomimetic effects
- it is approximately equipotent to morphine, the usual dose 10 mg i.m.
- the onset of effect after parenteral administration is 2-3 min/i.m, or 15 min/i.v.
- the duration of action is ~ 3-6 hrs
- its predominant site of action, like pentazocine, is the κ -receptors of the spinal cord
- respiratory depression is similar to morphine, however, like other agents in this group exhibits a **ceiling effect** and is reversed by naloxone

NB: unlike the other members in this group, nalbuphine **does not** elevate BP, HR, LVED pressure, PA pressure, or increased cardiac work in IHD patients

- nalbuphine is metabolised in the liver and the $t_{\beta/2} \sim 5$ hrs
- oral bioavailability is ~ 20-25%

BUPRENORPHINE

- is a semisynthetic, highly lipophilic derivative of the opium alkaloid thebain
- approximately 25-50 times as potent as morphine, usual dose ~ 0.3-0.6 mg
- like the preceding agents, buprenorphine is a partial agonist at μ -receptors, however it has a very **high affinity** for these and the respiratory depression, while showing a **ceiling effect**, is poorly reversed by naloxone
- produces analgesia and other effects similar to morphine, including CVS
- it is well absorbed from most routes, including the sublingual
- peak blood concentration appear at 5 min/i.m., and at 2 hrs/s.l., or oral
- plasma protein binding is ~ 96%
- plasma half-life is ~ 3 hrs, however, the duration of action is longer, sometimes up to 6 hrs, probably due to tissue binding
- both N-dealkylation and conjugation occur in the liver, however most of the drug is excreted unchanged in the faeces
- may produce a delayed onset withdrawal syndrome several days after cessation of the drug

OPIOID ANTAGONISTS

- under ordinary circumstances the drugs in this group produce few effects unless drugs with opioid agonist activity are given prior
- however, when the endogenous opioid system is activated, as in shock, the administration of an antagonist along has demonstrable effects
- the common drugs in this group include levallorphan, nalorphine and naloxone
- the common structural difference with these agents is substitution at the N₁₇ moiety for a larger group,



- a. morphine → nalorphine
- b. levorphanol → levallorphan
- c. oxymorphone → naloxone

- occasionally congeners are produced which are competitive antagonists at μ -receptors, but have partial agonist actions at other receptors
- ***nalorphine*** was the first such agent produced in the search for a nonaddictive opioid analgesic, however, the marked ***dysphoria*** produced limited its clinical usefulness as an analgesic
- nalorphine did, however, remain the treatment of choice for opioid overdose for many years
- levallorphan has similar actions but is far more potent than nalorphine
- other congeners, such as naloxone, have apparently no agonist action and appear to bind to all classes of opioid receptors, albeit with different affinities

NALOXONE

- as stated, is the ***N-allyl derivative*** of the opioid analgesic ***oxymorphone***
 - it possesses almost no agonist activity and if administered *de novo* has almost no clinical effect
 - it antagonises the effects of the opioid analgesics and the agonist/antagonist group such as pentazocine and butorphanol but ***not*** buprenorphine (NB: MCQ)
 - the duration of action after i.v. administration is short ~ ***20 min***
 - naloxone is rapidly metabolised in the liver, primarily by glucuronidation
 - very high first pass metabolism (***bioavailability*** ~ ***2%***) necessitating i.v. administration
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- naloxone is the drug of choice for the treatment of opioid respiratory and CVS depression
 - the usual adult dose is 0.1-0.4 mg i.v.
 - also available for neonatal use, usual dose 0.01 mg/kg (now use adult strength)
 - due to the short duration of action monitoring is essential and repeated doses may be required