OPIOIDS

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Mechanism of action

OPIOIDS

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

Opiate Receptors In The CNS

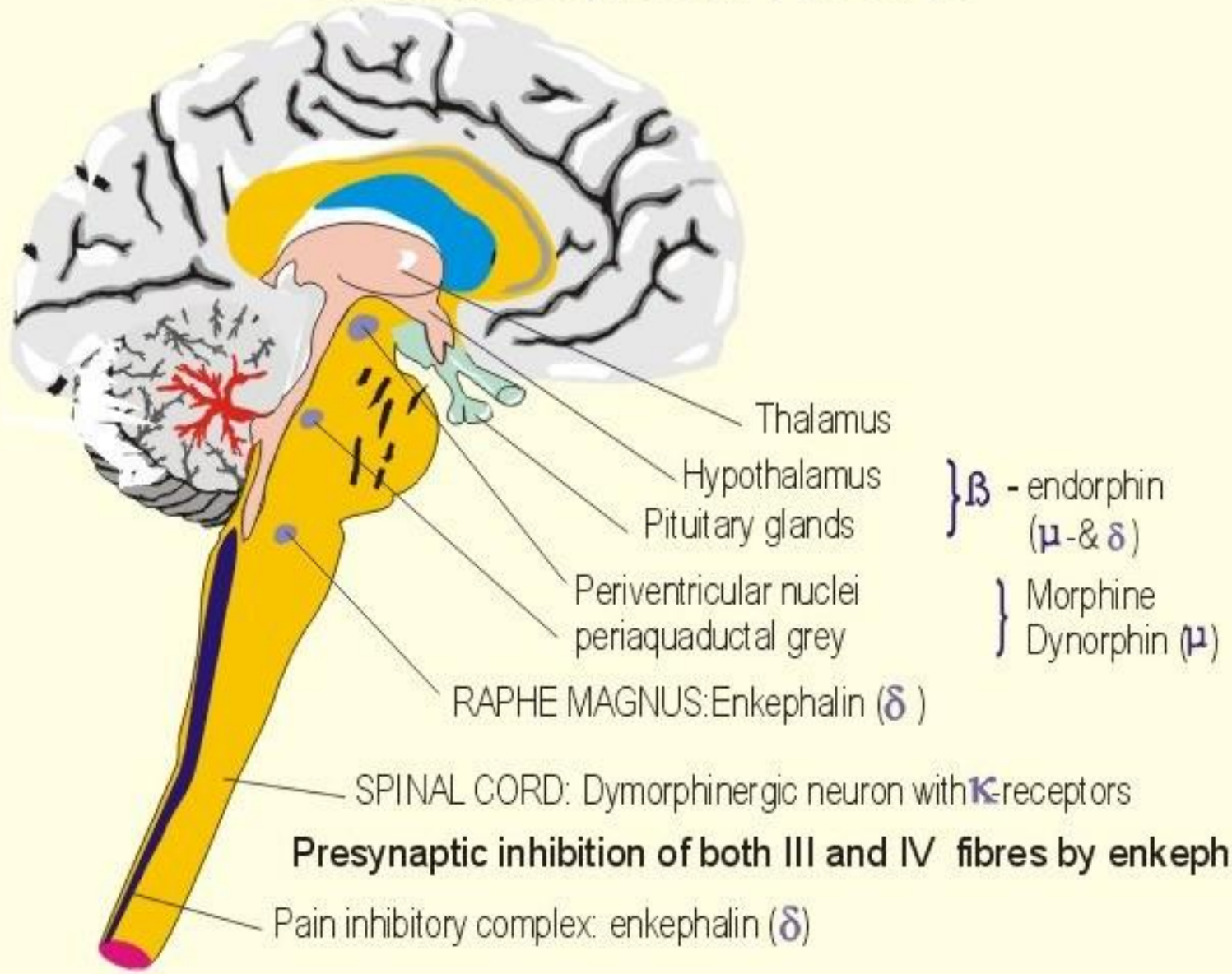
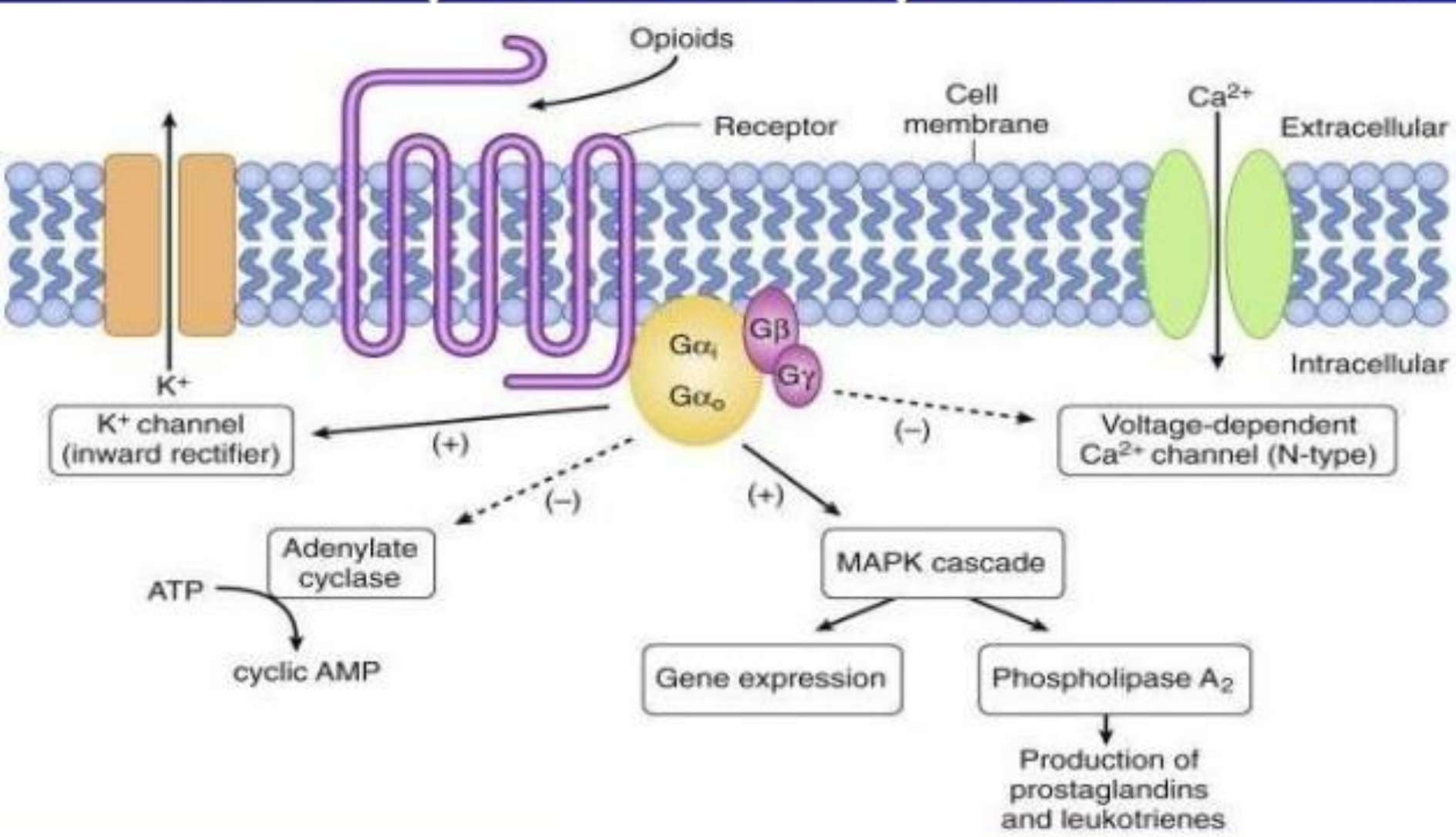


Fig. 3-10

KMc

Mechanism of action of Opioid Receptors



Opioid receptors

- MOP - μ (mu) opioid peptide receptor
- KOP - κ (kappa) opioid peptide receptor
- DOP - δ (delta) opioid peptide receptor
- NOP (nociceptin **orphanin** FQ peptide receptor) completely antagonist

OPIOID RECEPTORS, THEIR ENDOGENOUS LIGANDS AND EFFECT PRODUCED ON RECEPTOR STIMULATION

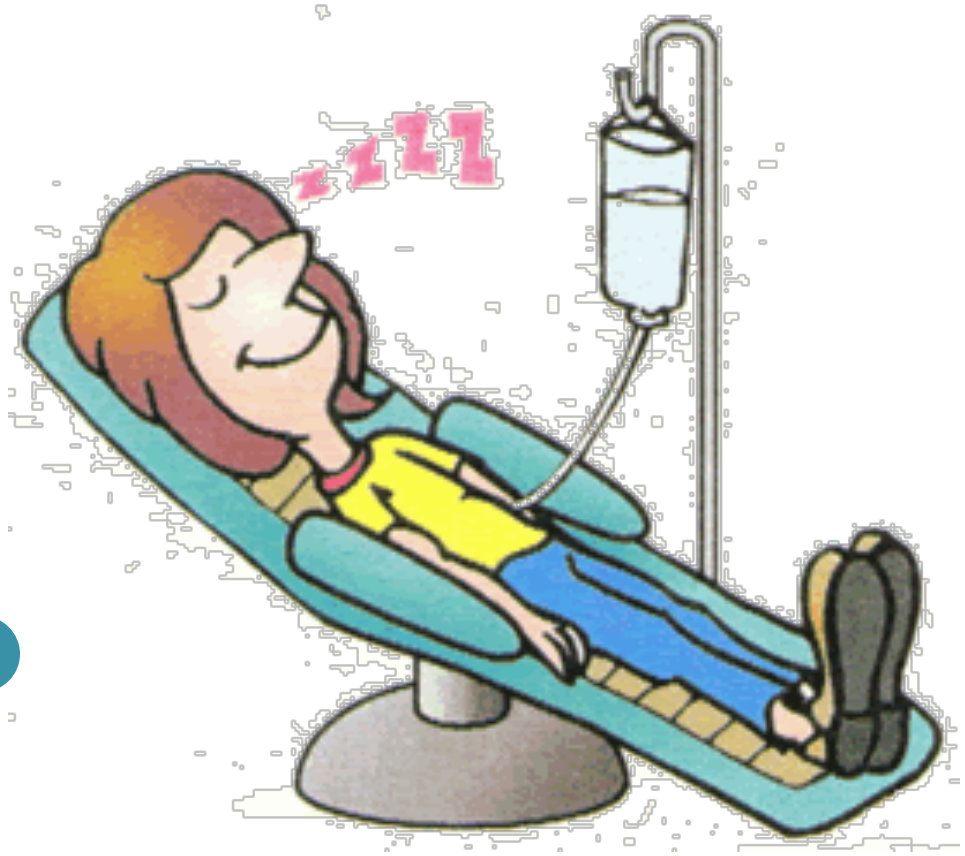
RECEPTOR	ENDOGENOUS LIGAND	EFFECT ON RECEPTOR STIMULATION
Mu(μ)	Endorrphin	Supraspinal analgesia (μ_1) Dependance (μ_2) Respiratory depression (μ_2) Constipation (μ2) , miosis (μ_2)
Kappa(κ)	Dynorphin	Spinal analgesia Sedation Miosis
Delta(δ)	Enkephalins	Respiratory depression

PHARMACOLOGICAL ACTIONS OF OPIOID AGONISTS

- Central nervous system
- Cardiovascular system
- Respiratory system
- Gastrointestinal System
- Endocrine System
- Ocular effects
- Histamine release and itching
- Muscle rigidity
- Immunity depressed after long-term opioid abuse
- pregnancy and neonates


Analgesia

Sedation



But not true hypnosis

Euphoria and Dysphoria

If there is no pain, morphine may cause restlessness and agitation (dysphoria)

Hallucinations

more common with KOP agonists, but morphine and other MOP agonists may also cause hallucinations

يعمل Receptor أكثر كاپا

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 a 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 diarrhea

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 depression

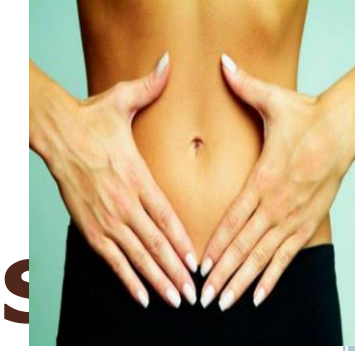
Respiratory rate falls more than the tidal volume and the sensitivity of the brain stem to carbon dioxide is reduced. Its response to hypoxia is less affected but if hypoxic stimulus is removed by supplemental oxygen then respiratory depression may be augmented.

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 Sys

- 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)

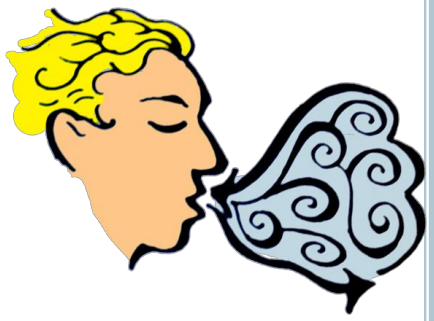
Histamine release and itching

- 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.

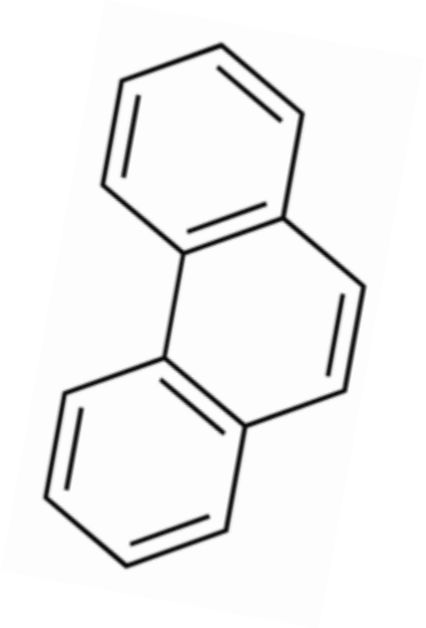
PREGNANCY AND NEONATES

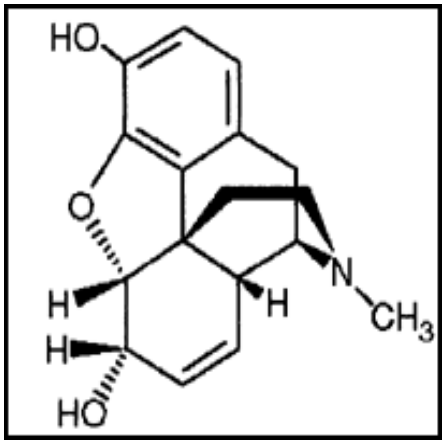
- **All opioids cross the placenta and if given during labour, can cause neonatal respiratory depression.**

- **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.**

Lets talk about some common drugs





Morphine

Morphine is a <u>naturally</u> occurring phenanthrene derivative

Remember <u>low lipid soluble</u>

- 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, Morphine may be given epidurally at 10% and intrathecally at 1% of the parenteral dose.

- Morphine is extensively metabolized by the gut wall and the liver to:
  - ✓ morphine-3-glucuronide (M3G) >> 70%
  - ✓ morphine-6 glucuronide (M6G) >> 10%

10-20 times more potent than morphine

  - ✓ sulphate conjugates

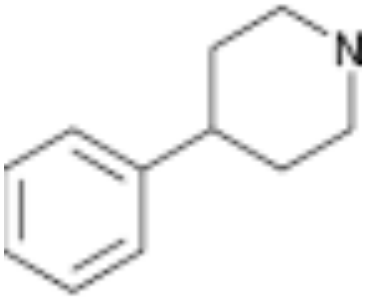
- M6G normally excreted in urine >> It accumulates in renal failure and accounts for increased sensitivity to morphine.

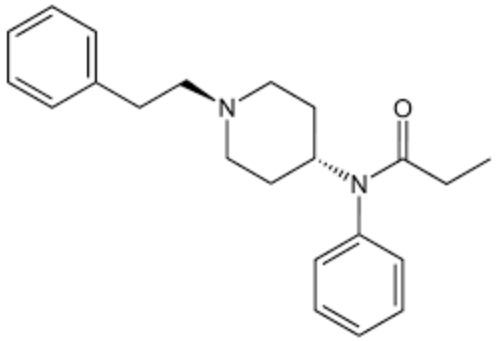
- Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity.

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

• 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





Fentanyl

synthetic phenylpyperidine derivative and is 100 times more potent than morphine

500 times more lipid soluble

- 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.

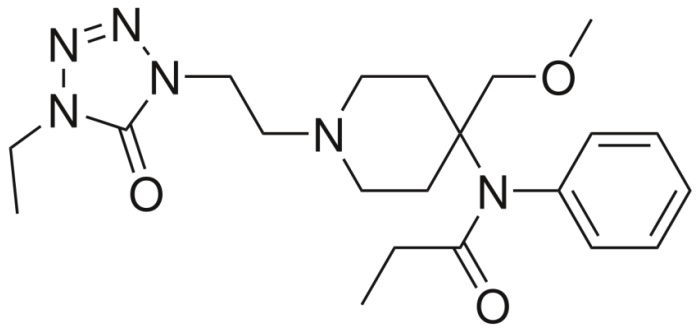
• Fentanyl is **500** times more lipid soluble than morphine, consequently it is rapidly and extensively distributed in the body (volume of distribution 4 L.kg-1). At small doses, plasma and CNS concentrations may decrease quickly to below an effective level during the rapid distribution phase.

• 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.

- 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.



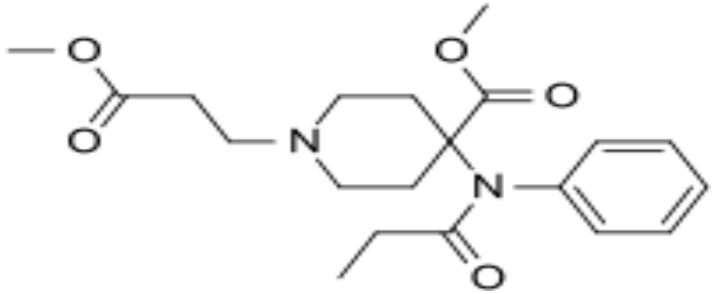
ALFENTANIL

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

Quicker onset and shorter duration

- Alfentanil can 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.



REMIFENTANIL

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

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

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

- 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.

Pethidine (mepiridine)

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

orally (50-150mg)

SC (50-100mg)

IM (50-100mg)

IV (25-100mg)

can be repeated every 4 hours.

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

- It is metabolized in the liver by ester hydrolysis to:

✓ norpethidine (At higher concentration can produce hallucination and convulsions)

✓ pethidinic acid (inactive compound.)

they are excreted in the urine and therefore accumulate in renal failure.

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

- 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, shivering , diaphoresis , ataxia , hyperrefelxia , confusion , convulsion and coma may occur.

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Naloxone

ANTAONIST EFFECT

The usual dose is 200-400mcg intravenously, titrated to effect. Administered slowly to avoid reactive pulmonary hypertension with the development of acute pulmonary edema probably from antagonism of endogenous opioid effects.

Smaller doses (0.5-1.0mcg.kg-1) may be titrated to reverse undesirable effects 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. **(10 mcg.kg-1 in neonate)**

Caution must be used in opioid addicts as giving naloxone may cause an acute withdrawal state with hypertension, pulmonary edema and cardiac arrhythmias. Antanalgesic effects may be observed in opioid naïve subjects who are given naloxon


THE END