## B5 - Opioid agonists & antagonists

- opioids are unique in producing analgesia without loss of touch, proprioception or consciousness.
- convenient classification = agonists (morphine), agonist-antagonists (pentazocine) & antagonists (naloxone)

Opium - derived from the Greek word for juice (the juice from opium is the source of 20 distinct alkaloids)

Opiate - drugs derived from opium

Narcotic - derived from Greek work for stupor & traditionally has been used to refer to potent morphine-like analgesics with the potential to produce physical dependence.

Opioid - all exogenous substances, natural & synthetic that bind to opioid receptors and produce agonist effects.

### (a) To describe the opioid receptor

- classifed into mu, delta & kappa receptors
- belong to the family of guanine (G) protein-coupled receptors.
- agonists -> inhibit adenyl cyclase -> decrease conductance of voltage-gated Ca2+ channels or open K+ channels -> hyperpolarisation -> prevention of excitation or propagation of action potentials.
- also modulate the phosphoionositide-signaling cascade phospholipase C.
- also may regulate the functions of other ion channels including the NMDA receptor

See diagram - mu receptor on laptop

*MU*

- single gene
- 6 types of receptor
- principally responsible for supraspinal & spinal analgesia.
- ? mu1 = analgesia
- ? mu2 = hypoventilation, bradycardia, physical dependence.
- exogenous mu receptors agonists = morphine, meperidine, fentanyl, sufentanyl, alfentanyl & remifentanyl.
- naloxone = mu receptor anatonist (competitive inhibition)

*KAPPA*

- endogenous agonist = dynorphin
- produce inhibition of neurotransmitter release via N Ca2+ channel-linked receptors.

*DELTA*

- endogenous agonists = enkephalins.

**(b) To describe the mechanisms of action of opioids.**

- act as agonists at opioid receptors at:

(1) presynaptic in CNS
(2) post-synaptic sites in the CNS (brainstem & spinal cord)
(3) peripheral tissues (activation of peripheral afferent neurons)

- opioid receptors are activated by 3 endogenous peptide ligands - enkephalins, endorphins, dynorphins.
- opioids mimic their action by binding to the receptors -> activate pain-modulating systems.
- only ionized & levorotary forms of opioid exhibit agonist activity.

- primary effect of receptor activation = decrease in neurotransmission via inhibition of transmitters (Ach, dopamine, norephinephrine, substance P)

- this is through (1) increase in K+ conductance -> hyperpolarisation (2) Ca2+ inactivation
- both -> decrease in neurotransmitter release.

- in brain: periaqueductal gray matter of brainstem, amygdala, corpus striatum & hypothalamus)
- in spinal cord: substantia gelatinosa

**(c) To describe the actions of agonitsts, partial agonists, mixed agonists-antagonists & antagonists.**

**Agonists**

- ie. morphine, fentanyl, meperidine (pethidine), sufentanil, alfentanil, remifentanil

- have intrinsic activity to produce some effects of endogenous compounds when they interact with the receptor.

**E = alpha[DR]**

E = amount of effect
Alpha = drugs intrinsic activity
DR = quantity of the drug receptor complex

Full agonist = will produce maximal response at full receptor occupancy (morphine) - efficacy 1.

**Partial agonist**

= will produce a lower maximal response at full receptor occupancy (tramadol) - efficacy 0 to 1.

Pure antagonists = efficacy 0.

- the difference between full & partial agonists depends on response & receptor occupancy.
- a partial agonist may be more, less, or have the same potency than a full agonist **-> potency = independent factor**

**Mixed agonists-antagonists**

- ie. pentazocin, butorphonol, nalbuphine, bremazocine, dezocine, meptazinol.

- drugs that produce antagonistic effects at one receptor & then agonist activity at others.
- ie. antagonism @ mu & agonism @ kappa - pentazocine, nalorphine.
- there is a ceiling to the max effect possible.

**Antagonists**

- ie. naloxone, naltrexone, naimefene

- occupy a receptor without causing activation and yet preventing the response to an agonist (produce a competitive blockade).

**(d) To describe the pharmacokinetics of different routes of administration & clinical implications with reference to:**

**- intravenous & PCA**
**- intramuscular & subcutaneous**
**- spinal**
**- epidural**
**- transdermal**
**- oral**

**IV & PCA**

See table - Opioid PK & PD

- after dose -> arterial plasma concentration rises to a peak within one circulation time
- this is dependent on the degree of pulmonary uptake (75% fentanyl, 4% morphine)

- plasma concentration declines rapidly due to **distribution** & **liver metabolism**.

- most opioid have a **large Vd** (except remi where Vd = 0.5L/kg)

- most have a **poor clearance** (< than 20mL/kg/min) except remi (Cl 40mL/kg/min)

**IM & SC**

- PK altered by differences in muscle blood flow & doses inadvertent subcutaneous fat injection.
- morphine 0.2mg/kg -> peak plasma concentration @ 45min

**Spinal**

- mu receptor action in substantia gelatinosa of spinal cord.
- **NO** protein binding -> small dose reaches high concentration when introduced into CSF.
- bulk flow carries drug rostrally to ventricular system in 24hrs.
- when reaches 4th ventricle -> respiratory depression.
- morphine (hydrophilic) -> respiratory depression 8-12hrs post
- fentanyl (more lipophilic) -> rapidly taken up by blood vessels, spinal cord & nerves -> respiratory depression usually takes place within 30min.

**Epidural**

- PK limited by:

(1) access to CSF - dura, arachnoid granulations & posterior radical arteries -> perfuse dorsal horn.
(2) lipid buffering
(3) more extensive uptake into systemic circulation

- larger doses needed (5-10x spinal dose)
- systemic side effects more likely
- same rostral spread once in CSF

- LA + opioid -> reduces the side-effect of the LA (hypotension, sensory & motor block, nausea, urinary retention)
- also produces synergy.

**Transdermal**

- requires:

**(1) high solubility in water**
**(2) high solubility in oil**
**(3) high potency**
**(4) little or no skin irritation**

- ie. transdermal fentanyl
- eliminates first pass metabolism by the lungs & liver.
- improves patients compliance & gives consistent analgesia.
- plasma fentanyl levels plateau @ 18hrs.

**Oral**

- first pass metabolism a factor here
- 40% bioavailability of morphine

**(e) To describe the PKs of IV opioids & their clinlcal applications with particular reference to morphine, fentanil, alfentanil & remifentanil.**

See drug profiles later

**(f) To describe the pharmacology of opioids deposited in the epidural space or CSF.**

See above (d)

- mu receptors in the substantia gelatinosa in the spinal cord.
- analgesia not associated with sympathectomy, sk muscle weakness or loss of proprioception.
- analgesia is dose related (epidural 5 - 10 x spinal)
- specific for visceral rather than somatic pain

**Spinal**

See above (d)

**Epidural**

- diffusion across dura -> mu receptors on spinal cord + systemic absorption.

*PK*

Uptake

- epidural fat
- systemic absorption
- diffusion across dura into CSF (lipid solubility)

- fentanyl = 800 x as lipid soluble as morphine.
- peak effect in 20min

- sufentanil = 1600 x as lipid soluble as morphine
- peak effect 6min

- morphine
- peak effect 1 - 4hrs

Distribution

- epidural space has extensive venous plexus -> vascular absorption is extensive.

- fentanyl = [plasma] peak 10min
- sufentanil = [plasma] peak 5min
- morphine = [plasma] peak 15min

- addition of epinephrine increases post-operative analgesia.

- lipid solubility determines how far cephalad the opioid will migrate

*PD*

- dose dependent
- 4 common side effects:

(1) pruritis - cephalad migration of opioid & interaction with opioid recectors in trigeminal nucleus.

(2) urinary retention - action of opioid on opioid receptors in sacral spinal cord -> decrease in parasympathetic tone -> detrusor muscle relaxation -> increase in bladder capacity.

(3) respiratory depression -> two peaks (1) 2 hr post dose (2) 8-12hrs post

(4) nausea & vomiting

**(g) To provide a detailed account of the pharmacodynamics of individual opiods & their clinical applications with particular reference to:**

**- morphine**
**- pethidine**
**- codeine**
**- fentanyl**
**- alfentanil**
**- remifentanil**
**- sufentanil**
**- methadone**
**- oxycodone.**

**Morphine**

- unripe seeds of *papaverum semniferin*
- can be synthesized but more easily derived from opium

Chemical - a phenantherene derivative

## Uses

(1) premed
(2) analgesic - viseral & sk muscle
(3) LVF
(4) symptomatic treatment of diarrhoea (combined with kaolin)

## Structure - see diagram

## Physiochemical

- pKa 7.9
- octane:H2O coefficient 1.4 (low lipid solubility)

## Preparation

- tablets
- syrup
- suppositories
- solution - clear, colourless solution for injection
- no preservative

## Route

- PO
- PR
- IV
- S/C or IM
- intrathecally\epidurally
- nebulised

## Dose

### - route - dose, frequency, time to peak effect

- PO - 5 to 20mg Q4 hrly,
- PR - 15 to 30mg Q4 hrly
- IM/SC - 0.1 to 0.2mg/kg Q4 hrly, 60min
- IV 0.05 - 0.1mg/kg  Q4 hrly, 30min
- nebulised: peak onset 30min

## PK

*Absorption*

- bioavailability PO = 40% due to extensive first pass metabolism
- 20% unionised

*Distribution*

- 30% protein-bound in plasma
- Vd 4 L/kg
- distributes between CSF & plasma slowly

*Metabolism*

- hepatic
- metabolised to morphine-3-glucuronide (effect on arousal), morphine-6-glucuronide (effect on analgesia) & normorphine.
- be aware in hepatic failure -> may precipitate encephalopathy

*Excretion*

- mainly urinary
- 10% -> faeces
- clearance 20mL/min/kg
- t1/2 3 hrs
- accumulation takes place in renal failure

PD

*Main action* - analgesia & respiratory depression

*Mode of action*

- mu & kappa receptor agonist
- increase intracellular Ca2+ -> increased K+ conductance -> hyperpolarisation of excitable cell membranes -> decrease in pre & post synaptic responses
- reversed by naloxone

Onset = 6min
Peak effect = 20min

*CVS*

- orthostatic hypotension secondary to decrease in SVR via histamine release
- high doses = bradycardia

*RESP*

- respiratory depression

- decreased response to hypoxia & hypercarbia
- antitussive action
- bronchospasm (high doses)

*CNS*

- potent analgesic agent
- drowsiness
- miosis c/o stimulation of Edinger-Westphal nucleus
- hallucinations
- seizures & rigidity (high doses)
- decreases MAC of volatiles

*GI*

- decreases GI motility -> increased H2O reabsorption -> constipation
- decreases secretions (gastric, bilary & pancreatic)
- spasm of sphincter of Oddi
- N & V

*GU*

- increases tone in ureters, relaxation of detrusor muscle & sphincter -> retension

*Metabolic*

- diaphoresis
- pruritis
- increase in ADH secretion -> water retension -> hyponatraemia
- decrease in adrenal steroid secretion

## Pethidine

### Chemical

- synthetic opioid agonist derived from phenylepiperidine
- 1/10$^{th}$ as potent as morphine

### Uses

(1) premed
(2) analgesic in the management of moderate to severe pain
(3) antispasmotic (renal & biliary colic)

### Structure

- see diagram
- share several structural features that are present in LA (ie. tertiay amine, ester group &  lipophilic phenyl group)

Preparation

- tablets: 50mg
- IV: clear, colourless solution, 10 to 50mg/mL of pethidine HCL

Routes - IV, IM, PO, epidurally

Doses

- route, dose, time to onset

- PO: 50-150mg Q4hrly, 15min
- IM: 25-150mg Q4hrly, 10min
- IV: 25-100mg Q4hrly
- epidurally: 25mg

- duration of action 2-4hrs

PK

*Absorption*

- PO bioavailability = 60%
- IM bioavailability = 100%

*Distribution*

- 70% protein bound
- Vd = 5L/kg
- crosses the placenta

*Metabolism*

- hepatic
- N-demethylation to norpethidine -> hydrolysis to pethidinic acid -> hydrolysis to norpethidinic acid.
- norpethidine accumulates in renal failure, is active and has convulsant properties.

*Elimination*

- 20% unchanged in urine (pH dependent)

- norpethidine excreted in urine
- Cl = 20mL/min/kg
- t1/2 = 4hrs

PD

*Main action* - analgesia & respiratory depression

*Mechanism of action*

- mu & kappa agonist
- increases intracellular Ca2+ concentration -> increases K+ conductance -> hyperpolarisation -> decreased pre & post synaptic responses.

*CVS*

- orthostatic hypotension (histamine release & alpha-adrenergic blockade)
- mild tachycardia (anticholinergic effects)

*RESP*

- potent respiratory depression
- obtunds ventilatory response to hypoxia & hypercarbia
- chest wall ridgity
- little antitussive activity

*CNS*

- analgesia
- more euphoria than morphine
- less nausea & vomiting
- miosis
- when administered intrathecally blocks Na+ channels

*GI*

- decreases rate of gastric emptying
- less marked increase in bile duct pressure & intestinal activity than morphine

*GU*

- decreases ureteric tone
- may increase the amplitude of uterine contraction

*Metabolic*

- increases ADH secretion
- decrease adrenal steroid secretion

*Other adverse effects*

- may precipitate severe hypertensive episodes in patients receiving MAOIs
- reduces MAC
- inhibits post-anaesthetic shivering

## Codeine

Chemical - naturally occurring phenanthrene alkaloid which is a methylated morphine derivative.

Uses

(1) mild to moderate pain
(2) diarrhea & excessive ileostomy output
(3) antitussive
(4) analgesia for HI patients

Preparation

- tablets
- syrup
- clear, colourless solution for injection
- mixed preparations with paracetamol, ibuprofen or aspirin

Routes - PO, IM, PR

Doses

- PO & IM: 30-60mg Q 4-6hrly, peak concentration = 60min
- PR: 1mg/kg

PK

*Absorption* - bioavailability = 70%

*Distribution*

- 7% protein bound
- Vd 5 L/kg

*Metabolism*

- hepatic by 3 methods in CYP2D6

(1) glucuronidation (20%) -> codeine-6-glucuronide
(2) N-demethylation (20%) -> norcodeine
(3) O-demethylation (20%) -> morphine

*Elimination*

- 20% unchanged
- Cl = 98 L/hr
- t1/2 = 3hrs
- reduce dose in renal failure

PD

*Main action* - analgesia, antitussive & decrease in GI motility

*Mechanism of action*

- 10% of drug metabolized to morphine -> analgesia via mu receptor
- antitussive effect seem mediated by codeine receptors

*CVS*

- do not administer IV -> profound histamine release -> cardiovascular collapse

*RESP*

- antitussive
- produces respiratory depression
- decrease in response to hypoxia & hypercarbia

*CNS*

- x 10 times less potent than morphine

*GI*

- marked inhibition of GI motility -> constipation
- N & V

**Fentanyl**

Chemical - a tertiary amine which is a synthetic phenylpiperidine derivative

- 100 x more potent than morphine.

Uses

(1) analgesia
(2) premed

Structure - see diagram

Physiochemical

- pKa 8.4
- 90% non-ionised @ pH 7.4
- octane:H2O partition co-efficient 955 (highly lipid soluble)

Preparation

- clear & colourless solution
- 50mcg/mL

- transdermal patch

- lozenges

Route

- IV
- Transdermal
- PO
- IM
- Epidural

Dose

- route, dose, time to onset

- IM - 50 to 100mcg (premed)
- IV - 1 to 100mcg/kg (induction or co-induction) - acts within 7 minutes
- Epidural - 50 to 100mcg

PK

*Absorption*

- PO bioavailability = 33%
- Transdermal = 50% @ 24/24, 88% @ 48/24, 94% @ 72/24

*Distribution*

- 95% protein bound
- Vd - 0.8 to 4.5 L/kg
- short duration of action secondary to redistribution
- lipid soluble -> crosses BBB -> rapid onset
- 75% of initial fentanil dose undergoes first pass pulmonary uptake.

*Metabolism*

- hepatic & intestine
- Cytochrome P450 34A
- N-dealkylation to norfentanyl -> hydroxylation to hydroxypropionyl derivatives.
- metabolites don't have appreciable analgesic activity

*Excretion*

- 10% urine (unchanged)
- clearance 20mL/kg/min
- distribution half-life = 10-30min
- elimination half-life = 2-6hrs
- decreased in hepatic impairment

PD

*Main action* - analgesia & respiratory depression

IV - acts for 30min to 6 hours (high dose)

*Mode of action*

- highly selective mu agonist
- increase intracellular Ca2+ concentration -> increases K+ conductance -> hyperpolarises excitable cell membranes -> decrease in membrane excitability in pre & post-synaptic responses.
- decreases MAC

*CVS*

- bradycardia (vagal in origin)
- Q, MAP, SVR, PVR, PCWP all unaffected

- obtunds cardiovascular response to laryngoscopy & intubation

*RESP*

- potent respiratory depressant
- decrease in RR & TV
- diminished response to hypoxia & hypercapnia
- potent antitussive agent
- chest wall rigidity - 'wooden chest' -> from mu receptor stimulation on GABA-ergic interneurons

*CNS*

- 80 x more powerful than morphine
- little hypnotic or sedative activity
- minor increase in ICP
- miosis

*GI*

- decreased GI motility
- decreased secretions
- contraction of sphincter of Oddi
- N & V

*GU*

- increases tone of ureters, bladder detrusor muscle & vesicular pressure -> retension

*Metabolic*

- no effect on WCC function
- does not increase the secretion of ADH

*Other adverse effects*

- secondary peak of fentanyl may occur post-operately secondary to elution of muscle -> respiratory depression
- thermoregulation - reach a lower thermoregulatory threshold.
- pruritis: not due to histamine release (must be receptor mediated central mechanism as gets better with naloxone).

**Alfentanyl**

Chemical - a synthetic anilionopiperidine derivative

Uses

(1) analgesia
(2) sedation in ICU

Preparation - clear, colourless solution

Physiochemical

- pK 6.5
- octaine:H2O partition co-efficient = 130
- 1/10th as potent as fentanyl
- 1/3rd duration of fentanyl

Route - IV

Dose

- bolus: 10 - 50mcg/kg
- infusion: 0.5 - 1mcg/kg/min
- peak effect in 90 sec
- duration of effect 5-10min

PK

*Distribution*

- 90% protein bound
- Vd = 60L
- brief action due to small Vd

*Metabolism*

- hepatic
- N-dealkylation to noralfentanyl -> aromatic hydroxylation, demethylation, amide hydrolysis, acetylation -> conjugation to glucuronide.
- not effected by renal failure

*Elimination*

- 90% appears in urine unchanged
- clearance 5mL/min/kg
- distribution t1/2 = 15min
- elimination t1/2 = 100min
- erythromycin, fluconazole & diltiazem inhibits clearance

PD

*Main action* - analgesia & respiratory depression

*Mode of action*

- highly selective mu agonist

- see fentanyl for rest of information

**Remifentanyl**

Chemical - synthetic anilidopiperdine derivative

Uses - analgesia

- 20 x more potent than alfentanil
- 250 x more potent than morphine

Structure - unique opioid as has ester linkage

Physiochemical

- pKa 7.3
- 60% non-ionised at pH 7.4

Preparation

- clear, colourless solution
- glycine buffer (thus not to be used in epidurals or intrathecally)

Route - IV

Dose

- boluses: 1mcg/kg
- infusion: 0.0125-1 mcg/kg/min
- peak effect = 1 min
- rapid offset

PK

- small Vd, rapid clearance, low individual variability

*Distribution* - Vd = 0.5L/kg

*Metabolism* - rapid ester hydrolysis by plasma esterases (nonspecific) -> carboxylic acid derivative
- independent of renal & hepatic function.

*Excretion*

- urine
- clearance 3 L/min!
- elimination t1/2 = 15 min
- independent of renal & hepatic function

PD

*Main actions* - analgesia & respiratory depression

*Mode of action* - see fentanyl

*CVS* - decreases MAP and HR by 20%
*RESP* - see fentanyl
*CNS* - see fentanyl
*GI* - low incidence of PONV

**Sufentanil**

Chemical - phenylpiperidine which is thienyl derivative of fentanyl

Uses

(1) induction & maintenance of anaesthesia
(2) post-op analgesia

Preparation

- clear, colorless solution
- 50micrograms/mL of sufentanil citrate.

Routes - IV, epidural

Doses

- route, dose, time to onset, duration of effect

- IV: 1 to 50micrograms/kg, 1- 6min, 30min to 8hrs

- Epidural: 1- 100micograms/kg,

PK

*Distribution*

- 93% protein bound (predominately to alpha-1 acid glycoprotein)
- highly lipophilic
- Vd = 5 L/kg

*Metabolism*

- hepatic
- N-dealkylation at the piperidine nitrogen & by O-demethylation

*Elimination*

- 60% appears unchanged in urine (adjust in renal failure)
- 10% in bile
- Cl = 20mL/min/kg
- t1/2 = 2.2hr

PD

*Main action* - analgesia & respiratory depression

*Mechanism of action*

- highly selective mu agonist
- part of analgesic effect attributable to 5-HT release

- decrease in intracellular Ca2+ & increase in K+ conductance -> hyperpolarisation -> decrease in membrane excitability.

*CVS*

- little haemodynamic change
- HR & BP decrease
- venous pooling -> orthostatic hypotension

*RESP*

- respiratory depression
- chest wall rigidity

*CNS*

- 4000 x more potent than morphine for analgesia
- EEG: initial beta activity decrease & alpha activity increased -> alpha activity disappears & delta activity predominates
- no effect of ICP
- miosis

*GI*

- less nausea than fentanyl
- spasm of sphincter of Oddi

*Metabolic*

- obtunds stress response to surgery

## Methadone

Uses

(1) chronic pain
(2) opioid withdrawal

Preparation - racemic mixture with almost all the activity residing R isomer

Physiochemical

- pKa 9.3
- octane:water co-efficient = 116

Routes - PO, IM

Doses - 1mg methadone = 1mg heroin or 3mg morphine

PK

*Absorption* - bioavailability = 80%

*Distribution* - 90% bound

*Metabolism* - N-demethylation

*Elimination* - t1/2 = 35hours

PD

*Main action* - synthetic MU agonist

*CVS* - reduced sympathetic tone

*RESP* - depression similar to morphine

*CNS* - less euphoria than morphine, miosis

*GI* - constipation, biliary tract spasm

**Oxycodone**

Uses - moderate to severe pain

Preparation - PO: slow release tablets

Routes - PO

**Tramadol**

- 10 x less potent than morphine

Chemical - synthetic opioid of the aminocyclohexanol group

Uses - moderate to severe pain

Preparations

- racemic mixture of two enantiomers
- PO: 50-150mg
- IV: 50mg/mL

Routes - IV,IM & PO

Doses

- all routes: 50-100mg, Q 4-6hrs
- 1 to 3 mg/kg, Q 4-6hrs

PK

*Absorption* - bioavailability = 90%

*Distribution*

- Vd = 4 L/kg
- 20% protein bound
- 80% crosses the placenta

*Metabolism*

- 85% by demethylation in the liver
- 1 metabolite is active

*Excretion*

- 90% is excreted in urine
- 10% in faeces
- Cl = 8mL/min/kg
- t1/2 = 6hrs
- adjust frequency of dose in renal & hepatic impairment.

PD

*Main action* - centrally mediated analgesia

*Mechanism of action*

- non-selective agonist at mu, kappa & delta opioid receptors
- also inhibits 5-HT release
- analgesia partly from activation of descending serotonergic & noradrenergic pathways
- does not cause tolerance or addiction

*CVS*

- flushing
- hypertension on IV bolus

*RESP* - no effects

*CNS*

- convulsions reported (lowers seizure threshold)
- dizziness

*GI* - higher incidence of PONV

**(h) To describe the adverse effects of opioids. To describe the prevention & management of these adverse effects.**

-> treatment in blue

CVS

- no direct effects on the heart
- BP usually well maintained unless cardiovascular system is stressed (via histamine release & central vasomotor center depression) -> hypotension.

-> cautious dosing, IV fluids, pressors.

RESP

- **respiratory depression**
- **cough suppression** -> accumulation of secretions & airway obstruction -> atelectasis

-> cautious dosing

CNS

- **analgesia** of both sensory & emotional components
- **euphoria** -> lessens anxiety & distress
- **sedation** - drowiness & clouding of mentation
- little or not amnesia
- **miosis**
- **trunchal rigidity** (intensification of tone in the large trunk muscles, results from supraspinal interaction)
- **nausea & vomiting** via activation of the brainstem chemoreceptor trigger zone (may also be a vestibular component as can be related to ambulation)
- increase in plasma PaCO2 -> vasodilation -> **increase in ICP**.

-> cautious dosing, administration of antiemetic

GI

- constipation
- tone increased, and peristaltic waves decrease -> decreased transit time -> increased absorption of H2O -> constipation.

-> operients

- constrict biliary smooth muscle -> colic
- constriction of sphincter of Oddi -> reflux of bile & pancreatic enzymes

- caution of morphine in hepatic & renal impairment.

-> cautious dosing

GU

- renal function depressed by opioids (>? decrease in RBF)
- enhance renal tubular Na+ reabsorption.
- increase in sphincter tone -> urinary retention.

-> clinical assessment +/- catheter

- may prolong labor c/o decrease in uterine tone

Skin

- flushing, warming of skin -> sweating & pruritis

-> antihistamine (for sedation effects)
-> low dose naloxone dose

Neuroendocrine

- stimulate the release of ADH, prolactin & somatotrophin
- inhibit LH
- inhibits the release of ACTH and blocks part of the pituitary-adrenal response to surgical stress.
- fentanyl abolishes the hyperglycaemia response to surgery

Immunological

- may modulate lymphocyte proliferation, antibody production & chemotaxis

Tolerance & dependence

*Tolerance*

- does not usually mainfest until after 2-3wks of frequent exposure to ordinary theraputic doses.

*Physical dependence*

- accompanies tolerance to repeated administration of the opioid MU type.
- abstinence syndrome = rhinorrhoea, hyperventilation, hyperthermia, lacrimation, mydriasis, piloerection, yawning, chills, muscle aches, vomiting, diarrhoea, anxiety & hostility.
- time to onset varies - morphine, heroin (6-10hrs), pethidine (24hrs), methadone (2weeks)

Musculoskeletal

- trunchal ridgidity (mainly associated with alfentanil)

Thermoregulation

- opioids + volatiles -> decrease thermoregulatory threshold to 34.5 C.

Other adverse effects

- crosses the placenta -> baby may experience withdrawal once born.

-> diazepam for child & supportive care

**(i) To describe the potential adverse drug interactions between opioids and other agents.**

**Sedative-hypnotics**

- increased CNS depression (in particularly respiratory depression)

**Anti-psychotic tranquilizers**

- increased sedation
- variable effects on respiratory depression
- accentuation of cardiovascular effects (antimuscarinic & alpha blocking actions)

**MAO inhibitors**

- relative contraindication to all opioid analgesics -> hyperpyrexia coma
- also hypertension (pethidine)

**Other specific interactions**

- erythromycin, fluconazole & diltiazem -> inhiibit the clearance of alfentanil.

**(j) To describe the pharmacology of opioid antagonists.**

**Agents**

- naloxone
- naltrexone
- nalmefene

**Action**

- have relatively high affinity for the MU receptor & have a lower afinity for kappa & delta sites.

**Naloxone**

Chemical - a substituted oxymorphone derivative

Uses

(1) reversal of respiratory depression due to opioids
(2) diagnosis & treatment of opioid OD
(3) clonidine OD
(4) obestity
(5) septic shock

Preparation - clear, colourless solution of injection contains 0.02-0.04mg/mL

Routes - IV, I'M, SC

Dose

- IV: 0.1-0.2mg
- SC/IM: 0.2-0.4mg

- acts within 2 minutes
- duration of 20min

PK

*Absorption* - bioavailability 2% from oral route

*Distribution*

- 50% protein bound
- Vd = 2 L/kg

*Metabolism*

- hepatic
- conjugation to glucuronide

*Excretion*

- Cl = 25mL/min/kg
- t1/2 = 1 hr

PD

*Main action* - reversal of MU opioid receptor effects.

*Mechanism of action*

- competitive antagnism at mu, delta, kappa & NMDA receptors.

*CVS* - no effect

*CNS* - decreased tolerance to pain

*GI* - reverses spasm of sphincter of Oddi