

OPIOID AGONISTS AND ANTAGONISTS

- (a) *To describe opioid receptors.*
- (b) *To describe the mechanism of action of opioids.*
- (c) *To describe the actions of agonists, partial agonists, mixed agonists-antagonists and antagonists.*
- (d) *To describe the pharmacokinetics of different routes of administration and the clinical implications with reference to intravenous, oral, subcutaneous, intramuscular, transdermal and patient controlled administration.*
- (e) *To describe the pharmacokinetics of intravenous opioids and their clinical applications with particular reference to morphine, fentanyl, alfentanil and remifentanil.*
- (f) *To describe the pharmacology of opioids deposited in the epidural space of cerebrospinal fluid.*
- (g) *To provide a detailed account of the pharmacodynamics of individual opioids and their clinical applications with particular reference to morphine, pethidine, codeine, fentanyl, alfentanil, remifentanil, sufentanil, codeine, methadone and oxycodone.*
- (h) *To describe the adverse effects of opioids. To describe the prevention and management of these adverse effects.*
- (i) *To describe the potential adverse drug interactions between opioids and other agents.*
- (j) *To describe the pharmacology of opioid antagonists.*

(I) Overview of Opioids and Opioid Receptors:

Definition of opiates, opioids and narcotics:

“Opiate” – Naturally-occurring substance derived from opium that produces morphine-like properties (Eg. morphine, codeine, thebaine, papaverine, noscapine)

“Opioid” – Exogenous substance (natural and synthetic) that has an affinity for opioid receptors → can be classified as either an – (i) agonist (Eg. morphine, fentanyl, remifentanyl, pethidine), (ii) agonist-antagonist (Eg. buprenorphine) or (iii) antagonist (Eg. naloxone)

“Narcotic” – Potent morphine-like analgesics with potential to produce physical dependence

Structure-activity relationships of opioids:

Important to note:

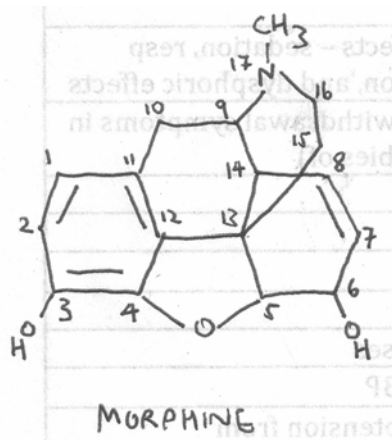
- All opioids are basic amines → ionisation of 3° amine N-group (on piperidine ring), which generally occurs at physiological pH, is vital for binding to anionic opioid receptor site
- Relationship b/t stereochemical structure and opioid potency exists → L-isomers are the most active (cf. D-isomers)
- Relationship b/t opioid receptor affinity and potency exists → ↑ affinity = ↑ potency

There are three types of opioids:

- (1) “Naturally-occurring opioids” → derived from naturally-occurring opium → include:
 - (i) Phenanthrenes alkaloids (Eg. morphine, codeine, thebaine)

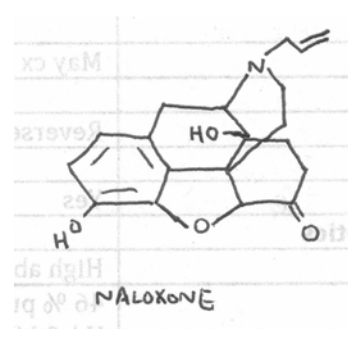
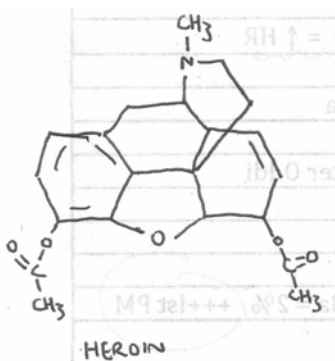
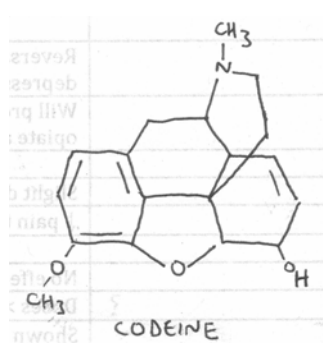
Important to note – Phenanthrene alkaloids have a complex ring structure that consists of:

- (1) Phenanthrene nucleus – 3-ring structure (with 14 C-atoms) that includes:
 - (i) Phenolic ring – Contains OH at 3-position → VITAL for opioid receptor activity
 - (ii) Cyclohexanol ring – Contains OH at 6' position
- (2) Piperidine ring – Contains a 3° amine N-group that is highly ionised (water-soluble) at physiological pH → VITAL for opioid receptor binding

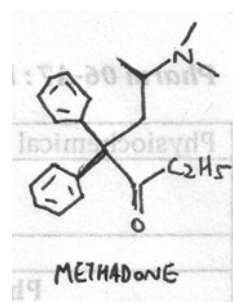
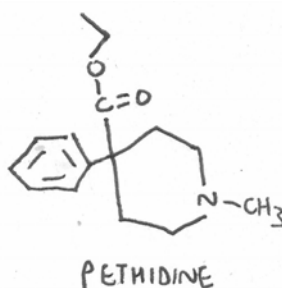
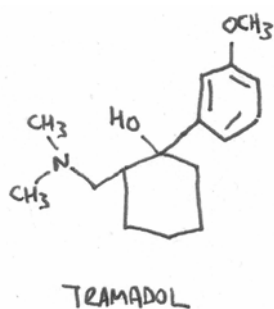
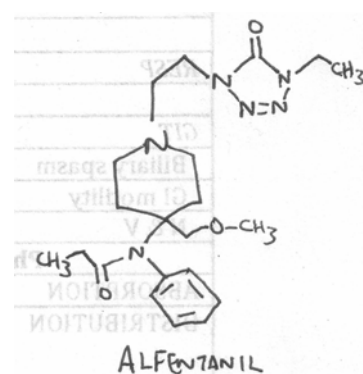
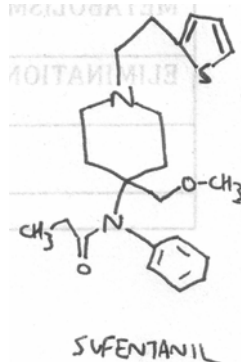
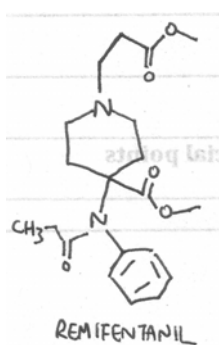
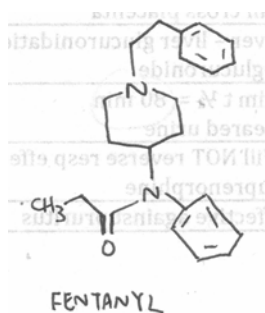


- (ii) Benzylisoquinoline alkaloids (Eg. papaverine, noscapine)
- (2) “Semi-synthetic opioids” → derived from simple chemical modification of morphine → they include:

- (i) Codeine – Methyl substitution of OH at 3-position (as methylmorphine) → produces a “pro-drug” that has ↑ lipid solubility and ↑ oral bioavailability (2° to ↓ hepatic FPM) but ↓ analgesic potency (as it needs to be metabolised to morphine)
- (ii) Heroin – Acetyl substitutions on OH of 3- and 6-positions (as diacetylmorphine) → produces a “pro-drug” that has ↑ lipid solubility and has ↑ analgesic potency once 3-position is deacetylated
- (iii) Naloxone – N-alkyl group on piperidine ring in oxymorphone is substituted for N-methyl group → produces opioid antagonist effect



- (3) “Synthetic opioids” → contain phenanthrene nucleus of morphine and are manufactured entirely by synthesis (cf. chemical modification of morphine) → include:
 - (i) Morphine derivatives (Eg. levorphanol)
 - (ii) Methadone derivatives
 - (iii) Benzomorphan derivative (Eg. pentazocine)
 - (iv) Phenylpiperidine derivatives (Eg. pethidine, fentanyl, remifentanyl, Etc.)



Opioid receptors and their mechanism of action:

There are 4 types of opioid receptors:

Receptor	Location	Effects	Receptor substrates
μ (mu)	Throughout CNS →	- Analgesia (supra-spinal and	Agonists – β-endorphins,

or MOP	brain (cerebral cortex, basal ganglia, amygdala, hypothalamus, periaqueductal grey of brainstem) and spinal cord (dorsal horn)	spinal) - Miosis - Respiratory depression ($\downarrow$ RR > TV 2° to $\downarrow$ chemoreceptor sensitivity to CO ₂) - CVS depression ($\downarrow$ HR and BP) - Constipation - Urinary retention - Euphoria/abuse potential - Physical dependence	morphine, pethidine, fentanyl, remifentanyl, Etc. Antagonists – Naloxone, naltrexone, nalmefene Agonists-antagonists – Buprenorphine
κ (kappa) or KOP	Throughout CNS also	- Analgesia (supra-spinal and spinal) - Dysphoria - Sedation - Miosis - Diuresis	Agonists – Dynorphin Antagonists – Naloxone, naltrexone, nalmefene Agonists-antagonists – Pentazocine, nalorphine, nalbuphine
δ (delta) or DOP	Less widely spread within CNS	- Analgesia (supra-spinal and spinal) - Respiratory depression - Urinary retention - Physical dependence	Agonists – Enkephalins Antagonists – Naloxone, naltrexone, nalmefene Agonists-antagonists – Pentazocine
NOP	Similar to μ receptor $\rightarrow$ analgesia acts at spinal and supraspinal levels (BUT hyperalgesia at low doses, and analgesia at high doses)		

Opioid receptor activation causes $\downarrow$ neuronal activity and neurotransmission via:

- (1) Pre-synaptic inhibition of NT release (Eg. substance P, ACh, NAd, Etc.) $\rightarrow$ *MAIN*
- (2) Post-synaptic inhibition of evoked synaptic potential

All opioid receptors are membrane-bound GPCR (Gi) $\rightarrow$ activation of the receptor causes inhibition of adenylyl cyclase $\rightarrow$ $\downarrow$ IC [cAMP] causing:

- (1) Opening of VG-K⁺ channels $\rightarrow$ $\uparrow$ K⁺ conductance and $\uparrow$ K⁺ efflux $\rightarrow$ hyperpolarisation causing $\downarrow$ neuronal activity
- (2) Closure of VG-Ca²⁺ channels $\rightarrow$ $\downarrow$ Ca²⁺ conductance and $\downarrow$ Ca²⁺ influx $\rightarrow$ prevents presynaptic nerve terminal exocytosis of NTs
- (3) $\downarrow$ cAMP-mediated gene expression

Note – (1) and (2) are immediate effects, while (3) is a delayed effect

Mechanism of opioid-mediated analgesia:

Important to note $\rightarrow$ opioids produce analgesia WITHOUT loss of touch, proprioception or consciousness

- Opioid receptors involved in pain transmission are located at pre- and post-synaptic sites in CNS (esp brainstem and spinal cord) and outside CNS in peripheral tissues

Important locations in CNS:

- Brain – Periaqueductal grey of brainstem (origin of descending inhibitory control pathway), cerebral cortex, basal ganglia, hypothalamus, amygdala
- Spinal cord – Dorsal horn/substantia gelatinosa (presynaptically on nociceptive (1°) neurons)

- Activation of these opioid receptors modulate transmission and integration of pain signals via:
 - (1) Inhibit neurotransmission of afferent pain signals at spinal cord dorsal horn → ↓ presynaptic NT release (esp substance P and glutamate) from nociceptive (1°) neuron nerve terminal onto 2° neurons → ↓ depolarisation of 2° neuron → ↓ afferent pain transmission
 - (2) ↓ cholinergic transmission in supra-spinal areas (esp in brain)
 - Note – They do not alter responsiveness of afferent nerve endings to noxious stimulation, nor do they impair conduction of nerve impulses along peripheral nerves

Aside – “Endogenous pain suppression system” → endogenous peptide opioids (enkephalins, endorphins, dynorphins) activate opioid receptors to produce anti-nociceptive effects

(II) Pharmacology of Neuraxial Opioids:

Overview of neuraxial opioids:

- Neuraxial opioids (epidural or intrathecal) can be used alone or in combination with a LA agent to manage acute or chronic pain → provides analgesia specific for visceral pain (cf. somatic pain)
- Characteristics of analgesic effects and side-effects are dependent on:
 - o (i) Choice of opioid used → varied effects due to differences in pharmacokinetics (Ie. fentanyl is 600x more lipid soluble cf. morphine → has faster onset but shorter duration of analgesia cf. morphine)
 - o (ii) Doses – Neuraxial opioid doses are significantly smaller cf. parental doses (with intrathecal dose 5-10x less than epidural dose) → analgesic effect and most side-effects are dose-related (Ie. ↑ dose = ↑ analgesia but ↑ adverse effects)

Important to note → only certain opioids can be used neuraxially as they need to be preservative-free (Eg. morphine, fentanyl, pethidine, sufentanil), otherwise spinal cord damage can occur

Mechanism of action of neuraxial opioids:

(1) Local effects on opioid receptors in spinal cord

Intrathecal → opioid in CSF diffuses across pia mater to directly activate opioid receptors in spinal cord
Epidural → opioid diffuses across dura/arachnoid mater into CSF first, then across pia mater to directly activate opioid receptors in spinal cord

(2) Effects at higher centres (esp in brainstem) via cephalad migration of CSF by bulk-flow

(3) Systemic effects due to absorption via epidural venous plexus → acts on opioid receptors elsewhere (similar to parental opioids)

Intrathecal → minimal amounts of opioid are absorbed systemically → clinically insignificant
Epidural → lipophilic opioids (Eg. fentanyl) are rapidly absorbed → thus, act almost entirely by systemic absorption (Ie. effects similar to parental opioids)

Pharmacokinetics of neuraxial opioids:

Epidural opioids:

- (i) Absorbed into epidural fat
- (ii) Diffuses across dural membranes into CSF → rate of diffusion is related to “Fick’s Law of diffusion” (determined esp by lipid solubility of opioid)
 - o Fentanyl is highly lipid-soluble → peak CSF [] at 20 mins
 - o Morphine is poorly lipid-soluble → peak CSF [] at 1-4 hrs only
- (iii) Absorbed systemically via epidural venous plexus → rate of diffusion is related to “Fick’s Law of diffusion” (determined esp by lipid solubility of opioid)
 - o Fentanyl is highly lipid-soluble → peak plasma [] at 5-10 mins
 - o Morphine is poorly lipid-soluble → peak plasma [] at 10-15 mins

Note – Plasma [] produced by epidural opioids ≈ plasma [] by IM opioids

Important to note – Adrenaline (vasoconstrictor) → ↓ systemic absorption of opioids, but NOT absorption into CSF

Intrathecal opioids:

- (i) Cephalad movement of opioids in CSF
 - o Opioids ascend intrathecal space in cephalad direction from lumbar region via bulk-flow of CSF → reaches cisterna magna in 1-2 hrs and ventricular system in 3-6 hrs
 - o Rate of migration dependent on lipid solubility of opioid:
 - Fentanyl (highly lipid-soluble) → limited migration due to rapid uptake into spinal cord
 - Morphine (less lipid-soluble) → extensive migration due to slow uptake into spinal cord

Important to note – Elimination $t_{1/2}$ of morphine in CSF $\approx$ that in plasma → intrathecal morphine given in lumbar region reaches cervical CSF within 1-5 hrs → risk of delayed respiratory depression

- (ii) Absorbed systemically via epidural venous plexus → clinically insignificant

Analgesic effects of neuraxial opioids:

Mechanism – Mainly caused by local effects on opioid receptors (esp μ receptors) in substantia gelatinosa of spinal cord → acts pre- and post-synaptically on 1° and 2° order nociceptive fibres to ↓ afferent transmission of pain signal

Effects – Segmental analgesia (esp for C-fibre-mediated dull pain >> A δ -fibre-mediated sharp pain) with sparing of motor effects and sympathetic effects (cf. regional LAs) → segmental distribution determined by lipid solubility of opioid (I.e. morphine has ↑ cephalad migration cf. fentanyl due to its low lipid-solubility → analgesia at more segments)

Note – Neuraxial opioids act synergistically with LAs, clonidine, ketamine to provide analgesia

Side-effects of neuraxial opioids:

Common side-effects include:

- (1) Pruritis
 - Most common side-effects (esp in obstetrics) → dose-related, occurs within few hrs of injection, and usually localised to face, neck and upper thorax (but can be generalised)
 - Due to cephalad migration of opioid in CSF → activates trigeminal opioid receptors (Nb. it is NOT caused by mast cell release of histamine!)
 - Treated with an opioid antagonist (Eg. naloxone) → Nb. anti-histamines work 2° to its sedative effects
- (2) Nausea and vomiting – Dose-related side-effect → due to stimulation of CTZ 2° to cephalad migration of opioid in CSF
- (3) Urinary retention
 - Common in young males → not related to dose
 - Due to opioid receptor activation in sacral spinal cord → inhibits sacral PNS outflow causing detrusor relaxation
- (4) Respiratory depression (* MOST serious side-effect *)
 - There are two potential phases:

- (i) Early respiratory depression (within 2 hr) – Due to systemic opioid absorption and subsequent interaction with opioid receptors in ventral medulla (I.e. ↓ ventilatory drive to CO₂) → generally involves a lipid soluble opioid (Eg. fentanyl)
- (ii) Delayed respiratory depression (> 2 hrs) – Due to cephalad migration of opioid and subsequent interaction with opioid receptors in ventral medulla → generally involves less lipid soluble opioid (Eg. morphine)

Note – Delayed respiratory depression tends to occur 6-12 hrs after neuraxial morphine (rarely occurs > 24 hrs)

- Risk factors for delayed respiratory depression:
 - (i) Use of ↑ doses or a low lipid-soluble opioid (esp morphine)
 - (ii) Concurrent use of opioid via an alternate route or a sedative (Eg. antihistamine, benzodiazepines, Etc.)
 - (iii) Lack of opioid tolerance
 - (iv) Advanced age

Note – Pregnancy reduces risk of delayed respiratory due to progesterone mediated ↑ MV

- Prevention → Monitor level of sedation (caused by hypercapnoea 2° to ↓ MV) and pulse oximetry to detect opioid-induced arterial hypoxaemia, and provide supplemental O₂
- Treatment involves opioid antagonist (Eg. naloxone)

(5) Sedation – Dose-related side-effect → due to μ receptor effects in reticular formation 2° to cephalad migration of opioid in CSF

Less common side-effects include:

- (1) Inhibition of shivering → hypothermia
- (2) Delayed gastric-emptying (due to local activation of spinal cord opioid receptors)
- (3) Miosis, nystagmus and vertigo (esp with morphine)
- (4) Reactivation of herpes simplex labialis virus causing trigeminal neuralgia (esp in obstetric patients 2-5 days after neuraxial opioid) → due to cephalad migration of opioid in CSF and interaction with trigeminal nucleus
- (5) Sustained erection and inability to ejaculate
- (6) Oliguria/H₂O retention → due to ADH release 2° to cephalad migration of opioid in CSF
- (7) ↑ CNS excitation/seizure (rare unless at ↑↑↑ doses) → non-opioid effect in brainstem 2° to cephalad migration of opioid in CSF → blocks glycine/GABA inhibition

Obstetrics issues with neuraxial opioids:

- (1) Respiratory depression of neonate → opioids are systemically absorbed in mother and transferred into neonate across placenta
- (2) Neuraxial opioids may affect progress of labour

Note – Opioid levels in breast milk is negligible

(III) Opioid Agonists:

Morphine:

Important to note → morphine is the “reference opioid” to which all others are compared to

Chemical structure: Naturally-occurring opioid → phenanthrene derivative

Mechanism of action: Mainly μ opioid receptor agonist (but little κ and δ agonist effects also)

Preparations:

- Clear, colourless solution (10-30 mg/mL) of morphine sulphate for IV/IM
- Clear, colourless solution (0.5 mg/mL) of preservative-free morphine sulphate for neuraxial use
- Tablets (5-200 mg) and syrup (2-20 mg/mL) for PO use
- Suppositories (15-30 mg) for PR use

Routes of administration and doses:

- PO – 5-20 mg q4h
- PR – 15-30 mg q4h
- SC/IM – 0.1-0.2 mg/kg q4h
- IV – 0.05-0.1 mg/kg q4h
- Intrathecal – 0.2-1 mg
- Epidural – 2-4 mg

Important to note → S/C route is avoided due to its ↓ lipid solubility → delays absorption

Important to note → neuraxial route carries risk of delayed respiratory depression due to its ↓ lipid solubility → causes morphine to enter spinal cord slowly, and thus allows it to be transported in CSF by bulk-flow up to midbrain to depress respiratory centres

Clinical uses:

- (1) Analgesia
 - o Used to (i) treat moderate-severe pain or (ii) adjunct to GA to provide intra- and post-operative analgesia
 - o Analgesic effect is best if given before noxious stimulus occurs → effective for dull, continuous and visceral pain (cf. sharp, intermittent and superficial pain)
- (2) Treat APO/LVF
- (3) Palliation

Pharmacokinetics:

Absorption	- PO – Absorbed 1°ly in small intestines > stomach (as it has ↑ % unionised in alkaline intestines cf. acidic stomach) → 30% bioavailability due to extensive hepatic FPM - IM/IV – Peak effects after 10-30 mins with duration of action of 3-4 hrs - Can be given PR and neuraxially also
Distribution	- V_D 3.5 L/kg - 35% protein binding - Weak base; pKa 8.0 (23% unionised at physiological pH) - ↓ lipid-solubility (1 octanol:H₂O coefficient) - Long effect-site equilibration time ($t_{1/2\text{ keo}}$) = 15-30 mins → due to ↓ lipid solubility and ↓ % unionised at physiological pH → poor BBB permeability (only < 0.1% crosses BBB) → results in slow onset/offset - Minimal first-pass pulmonary uptake (7%) but accumulates in liver, kidney and skeletal muscle → due to its ↓ lipid solubility
Metabolism	- Metabolised 1°ly in liver but also in kidneys: - (i) 1°ly by glucuronidation - o 85% → morphine-3-glucuronide (M3G) → inactive but may show some μ-receptor antagonism and cause arousal - o 10% → morphine-6-glucuronide (M6G) → similar μ-

	receptor affinity, pharmacology effects (esp analgesia and respiratory depression) and duration of action as morphine, BUT 13x ↑ analgesic potency (thus, contributes significantly to analgesic effects of morphine) - (ii) N-demethylation (5%) → normorphine Note – Morphine can be used with liver disease as compensatory ↑ renal glucuronidation of morphine occurs!
Excretion	- Urinary excretion of small amounts (1%) of unchanged morphine and its metabolites (esp M6G) - Some biliary excretion of unchanged morphine and its metabolites (10%) - Clearance 15 mL/min/kg - Elimination $t_{1/2}$ 1.5-3.5 hrs Note – Morphine should be avoided with renal failure as morphine and M6G will accumulate → ↑ risk of side-effects (esp respiratory depression)

Pharmacodynamic effects (including issues and side-effects):

Important to note → Effects of morphine are shared with other opioids mentioned below

- (1) Analgesia → Most effective if given BEFORE noxious stimulus occurs → relieves dull, continuous and visceral-type pain (cf. sharp, intermittent, superficial pain) and ↑ pain threshold (I.e. opposes hyperalgesia)
- (2) MAC sparing → ↓ volatile anaesthetic requirements
- (3) Respiratory effects:
 - (i) Dose-dependent respiratory depression
 - o Produces ↓ RR with compensatory ↑ TV → net ↓ MV (due to incomplete compensatory ↑ MV) → causes apnoea at excessive doses
 - o Due to direct inhibition of brainstem ventilatory centres → ↓ ventilatory drive to ↑ PaCO₂ and ↓ PaO₂

Note – CO₂ chemoreceptor sensitivity is affected more cf. O₂ → thus, supplementary O₂ removes hypoxic stimulus to breathe → potentiates respiratory depression
 - (ii) Anti-tussive effects → due to depression of medullary cough centre
 - (iii) ↑ AWR → due to direct bronchial SM effect and via histamine effect
 - (iv) Dose-dependent depression of ciliary activity
- (4) CVS effects:
 - (i) Mild bradycardia → due to ↑ CN X nuclei output and direct depression of SAN/AVN
 - (ii) Hypotension → due to histamine release (vasodilation) and bradycardia
 - (iii) Blunting of compensatory SNS responses → can trigger orthostatic hypotension
 - (iv) No direct myocardial depressant effects
- (5) CNS effects:
 - (i) Sedation (precedes onset of analgesia)
 - (ii) Euphoria (then dysphoria with ↑ doses)
 - (iii) Miosis → due to stimulation of Edinger-Westphal nucleus

- (iv) ↓ ICP and ↓ CBF
- (v) EEG changes → rapid α waves are replaced with slow δ waves ($\approx$ sleep EEG)
- (vi) Seizure-like activity ($\approx$ myoclonus or tonic-clonic) → BUT without seizure EEG activity
- (vii) Muscle rigidity (esp chest and abdominal wall) → due to opioid receptor interaction with DA and GABA pathways in substantia nigra/striatum → causes difficult PPV

Note – Opioids (esp morphine) should be used cautiously in patients with head trauma or ↑ ICP → can ↓ wakefulness, produces miosis, cause ↑ PaCO₂ (2° to respiratory depression) which can ↑ ICP, and head injury/↑ ICP destroys BBB which ↑ opioid sensitivity

(6) GI/GU effects:

- (i) Constricts gut sphincters and ↓ bowel mobility → constipation, delayed gastric emptying (aspiration risk) and delays oral absorption of drugs
- (ii) Sphincter of Oddi contraction → ↑ intrabiliary pressure → epigastric pain
- (iii) N/V → due to stimulation of CTZ via modulation of 5-HT/D2 receptors (Nb. stimulation of VC by opioids actually suppresses N/V!)
- (iv) ↑ ureteric tone
- (v) ↑ Bladder detrusor and vesical sphincter tone → urinary retention

(7) Histamine release:

- Causes – bronchospasms, hypotension, flushing of skin (esp face, neck and upper thorax), rash/urticaria (esp at IVI site), and pruritus (esp around the nose)
- There is a large individual variability in opioid-induced histamine release → tends to occur more with morphine (cf. fentanyl, remifentanyl, alfentanil, sufentanil), ↑ rates of administration
- Sequelae of histamine release can be prevented by H1RB/H2RB pre-treatment

(8) Endocrine effects:

- (i) Inhibits ACTH, PRL and GnRH hormones
- (ii) ↑ ADH release → ↓ Na⁺ and fluid retention

(9) Immune effects → prolonged opioid exposure causes immunosuppression (↓ development and function of various immune cells) → ↑ post-op. infection and cancer risk

(10) Obstetrics effects → opioids cross placenta readily into foetus → risk of neonatal respiratory depression (as foetal brains have ↑ opioid sensitivity 2° to immature BBB)

(11) Tolerance and dependence:

- (i) Tolerance:
 - o Occurs with repeated opioid use (Ie. ~ 2-3 weeks of morphine) → develop tolerance to analgesia, euphoria, sedation, respiratory depression, N/V (BUT NOT miosis and constipation)
 - o Cross-tolerance occurs between all opioids

Aside – Mechanism of tolerance → neuroadaptive changes with long-term opioid exposure, such as opioid receptor down-regulation, upregulation of IC cAMP systems, and ↑ synaptic [glutamate]/NMDA receptor activation

- (ii) Physical/psychological dependence
 - o Occurs with repeated opioid use (Ie. 2-3 weeks of morphine) → cessation of opioid causes “withdrawal syndrome” (yawning, diaphoresis, lacrimation, coryza, insomnia, restlessness, N/V, diarrhoea, abdominal pain) within 6-18 hrs (peaks 72 hrs) and lasts 7-10 days
 - o Requires opioid tolerance → often leads to opioid addiction

Important to note → Opioid-overdose:

- Characterised by respiratory depression (hypopnoea/apnoea), UAW obstruction (due to muscle flaccidity), miosis, sedation (leading to coma) → hypotension, seizures and mydriasis can occur with severe hypoxaemia
- Managed with mechanical ventilation with O₂ and careful administration of naloxone (while preventing withdrawal)

Pethidine:

Chemical structure: Synthetic opioid → phenylpiperidine derivative

Mechanism of action:

- Main effects as μ - and κ -opioid receptor agonists (Eg. analgesia, respiratory depression, Etc.)
- Also has other effects:
 - Anticholinergic effect (structurally similar to atropine) → causes ↑ HR, ↓ miosis (mydriasis possible), dry mouth and ↓ biliary spasms
 - α 2-adrenoceptor agonist → ↓ post-operative shivering
 - LA effect (structurally similar to LA agents) → blocks VG- Na⁺ channel when administered neuraxially and impairs nerve conduction

Clinical uses:

- (1) Analgesic for moderate-severe pain → it is 10x less potent and shorter acting (2-4 hrs) cf. morphine, BUT has faster onset (due to its ↑ lipid solubility)
 - (i) Treat post-operative pain – Can be used as IV PCA (but use > 3 days is a/w norpethidine toxicity) or given epidurally
 - (ii) Treat pain a/w labour and delivery
- (2) Treat post-operative shivering → due to its κ -opioid receptor and α 2 receptor effects
- (3) Antispasmodic agent to treat biliary/renal colic → due to its anti-cholinergic effects
- Note – Pethidine lacks antitussive effects

Preparations and doses:

- Tablet (50 mg) for PO use → 50-150 mg (Nb. unlike morphine, pethidine is well-absorbed in GIT and useful to treat acute or chronic pain states)
- Clear, colourless solution of pethidine HCl (10 or 50 mg/mL) for IM/IV use (25-100 mg) or epidural use (25 mg)

Pharmacokinetics:

Absorption	- PO – Well absorbed in GIT (unlike morphine) with 50% bioavailability - Can be given IM, IV or epidurally also
Distribution	- V_D 4 L/kg - 60% protein binding - Weak base; pKa 8.7 (5% unionised at physiological pH) - ↑ lipid-solubility (30 octanol:H₂O coefficient)
Metabolism	- Extensive hepatic metabolism (> 90%): - (i) Ester hydrolysis → pethidinic acid (inactive metabolite) - (ii) N-demethylation → norpethidine (active metabolite with 50% analgesic activity), which is then hydrolysed to norpethidinic acid Important to note – Norpethidine is toxic (causing confusion, hallucinations, grand-mal seizures) and its toxic effects CANNOT be reversed by naloxone → toxicity occurs when it accumulates, which occurs with prolonged or repeated use (as it has a long elimination t_{1/2} 15-20 hrs) or renal failure (as its is renally-excreted)

Excretion	- Urinary excretion of small amounts (1%) of unchanged pethidine and its metabolites → Nb. urinary excretion of pethidine is pH-dependent, as acidification of urine can ↑ pethidine excretion up to 25%! - Clearance 10-20 mL/min/kg; Elimination $t_{1/2}$ 3-5 hrs
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Issues and side-effects:

- (1) Analgesia → 10x ↓ potent cf. morphine
- (2) MAC-sparing of volatile-based anaesthesia
- (3) CNS effects → (i) ↑ euphoria cf. morphine and (ii) mydriasis (due to anticholinergic effects)
- (4) CVS effects → (i) tachycardia (due to anticholinergic effects) and (ii) orthostatic hypotension (due to histamine release and α blockade)
- (5) Respiratory effects → (i) ↑ potent respiratory depressant cf. morphine ($\downarrow$ TV > $\downarrow$ RR) due to ↓ ventilatory responses to hypercapnoea/hypoxia, (ii) chest/abdominal wall rigidity can occur (I.e. difficult PPV), and (iii) minimal antitussive effect
- (6) GI/GU effects → ↓ N/V, constipation, biliary tract spasm and urinary retention cf. morphine
- (7) ↓ histamine release cf. morphine
- (8) Anticholinergic side-effects → mydriasis, dry mouth, tachycardia, ↓ biliary tract spasm
- (9) Norpethidine toxicity → causes confusion, hallucinations, grand-mal seizures 2° to norpethidine accumulation, which occurs with prolonged/repeated use (due to its long elimination $t_{1/2}$ 15-20 hrs) or renal failure → toxicity is NOT reversed by naloxone
- (10) Interacts with MAOi/SSRIs to cause 5-HT syndrome (Eg. coma, labile circulation, hyperpyrexia, convulsions) → pethidine inhibits 5-HT reuptake centrally, which causes accumulation of 5-HT when used in conjunction with MAOi (inhibits 5-HT metabolism) or SSRI (inhibits 5-HT reuptake also)
- (11) Pethidine withdrawal occurs more rapidly than morphine withdrawal, BUT has a shorter duration and fewer ANS effects
- (12) At high doses → pethidine (i) saturates hepatic enzyme metabolism (I.e. zero-order kinetics), (ii) exerts -ve cardiac inotropy and (iii) causes histamine release
- (13) Obstetrics implications → transplacental transfer of pethidine (and less lipid soluble norpethidine) occurs when used for labour/delivery analgesia. $t_{1/2}$ β of pethidine and norpethidine is prolonged by 3x in foetus due to ↓ foetal clearance. But pethidine is thought to cause less respiratory depression in the neonate

Fentanyl:

Chemical structure: Synthetic opioid → phenylpiperidine derivative (related to pethidine)

Mechanism of action: Highly selective μ opioid receptor agonist

Preparations:

- Clear, colourless solution (50 ug/mL) of fentanyl citrate for IV or epidural use
- Transdermal patch (25-100 ug/hr)
- Lozenges (200 ug-1.6 mg)

Clinical uses and doses:

- (1) Analgesia:
 - IV fentanyl (IV 1-2 ug/kg) is used as intra- and post-operative analgesia → 75-125x more potent and faster onset (3-5 mins) cf. morphine, but shorter duration of action (30-60 mins)
 - Transdermal fentanyl (25-100 ug/hr) is used as post-operative analgesia → applied prior to induction for up to 72 hrs for sustained analgesia and ↓ parental opioid needs → BUT issue with slow onset (12-18 hrs to reach steady-state) and “depot effect” despite removal of patch (due to ongoing dermal absorption)

- (2) Minimises haemodynamic responses to surgical stimuli or laryngoscopy (IV 2-20 ug/kg) → needs to be given at least 3-5 mins prior to noxious stimulus and is not reliable (even at ↑ doses)
- (3) Obtund “metabolic stress” response to surgical stimuli (IV 50-150 ug/kg) → issues with chest wall rigidity, bradycardia and post-operative respiratory depression
- (4) Neuroleptanaesthesia when used with a major tranquiliser/hypnotic (IV 50-150 ug/kg)
 - Produces stable haemodynamics due to ability to suppress of metabolic stress response of surgery, and lack of histamine release and direct myocardial depressant effects
 - BUT issues with intraoperative awareness, post-operative respiratory depression, chest wall rigidity and unreliable obtundation of SNS response to noxious stimuli (even at very high doses)
- (5) Augment LA effects of neuraxial anaesthesia (10-25 ug intrathecal, 25-100 ug epidural)
 - Rapid onset of effect and minimal side-effects (esp delayed respiratory depression) as it diffuses rapidly from CSF into spinal cord (cf. morphine) due to its ↑ lipid solubility
 - BUT at large doses or repeated doses/infusion (epidural) → can cause side-effects (including respiratory depression)
- (6) Pre-medication to ↓ anxiety, sedation and facilitate induction of GA (oral transmucosal lozenges 15-20 ug/kg used 45 mins pre-induction) → used in children, but has issues of PONV and respiratory depression

Pharmacokinetics:

Absorption	- PO → absorbed in small intestine > stomach (as 1^oly unionised in alkaline intestines cf. acidic stomach). Poor bioavailability (33%) due to significant hepatic FPM - IV, IM, transdermal and neuraxial absorption also
Distribution	- V_D 4 L/kg - Large protein binding (84%), esp to A1AGP - Weak base; pKa 8.4 → 9% unionised at physiological pH - ↑↑ lipid solubility (955 octanol:H₂O coefficient) → ↑ potency and rapid onset of action as it can easily cross BBB - Effect-site equilibration time ($t_{1/2 \text{ keo}}$) = 6.8 mins → due to ↑ lipid solubility - Significant first-pass pulmonary uptake (75%) and uptake in adipose/muscle tissue → due to ↑ lipid solubility
Metabolism	Hepatic metabolism by CYP3A4 via: - (i) N-methylation of fentanyl (MAIN) → nor-fentanyl - (ii) Hydroxylation of fentanyl (minor) and nor-fentanyl → hydroxy-propionyl metabolites of fentanyl and nor-fentanyl Important to note → genetic polymorphism and drug-related inhibition/induction of CYP3A4 causes large interindividual variability in metabolism/clearance of fentanyl
Excretion	- Metabolites and small amounts (10%) excreted unchanged in urine → ↑ lipid solubility allows for ↑ tubular reabsorption of free drug - Clearance 15 mL/kg/min - Elimination $t_{1/2}$ 3-6 hrs → this is LONGER cf. morphine b/c fentanyl has a larger V_D (but same Cl) as morphine. It's ↑ V_D is due to its ↑ lipid solubility and distribution in lungs, fat and muscle tissues - CSHT (at 4 hrs) = 260 mins → ↑↑↑ with prolonged infusions or repeated doses due to saturation of inactive tissues, which retards rate of ↓ plasma [] when infusion is ceased as redistribution back into plasma is faster than its elimination by hepatic clearance

Important to note – Due to its pharmacokinetics, IV fentanyl has a:

- Rapid onset of action with slight lag (2-5 mins)
 - o Rapid onset due to its ↑ lipid solubility (900x ↑ cf. morphine) → crosses BBB rapidly
 - o Slight delay due to its effect-site equilibration time ($t_{1/2\text{ keo}}$) = 6.8 mins
- Variable duration of action:
 - o Low doses (< IV 3 ug/kg) → short duration of action (30-60 mins) as offset is due to its rapid redistribution to inactive tissues (I.e. lung, fat, muscle)
 - o Repeated doses (> IV 50 ug/kg) or infusions → prolonged duration of action (4-6 hrs) as fentanyl saturated in inactive peripheral tissues redistributes back into plasma, and offset is dependent on hepatic clearance ($t_{1/2\beta}$ = 3-6 hrs)

Pharmacodynamic effects (including issues and side-effects):

- (1) Analgesia → 75-125x more potent cf. morphine
- (2) MAC-sparing of volatile-based anaesthesia (by 50%) and ↑ muscle relaxation of ND NMBD
- (3) CNS effects:
 - o Myoclonus seizure-like activity (BUT no EEG spike-wave pattern) → due to depression of inhibitory neurons
 - o EEG changes – Initial ↓ β -activity and ↑ α -activity → α -activity disappears and δ -activity predominates
 - o Causes miosis (due to effects at Edinger-Westphal nucleus)
- (4) CVS effects:
 - o Bradycardia of vagal origin due to blunting of carotid BRR (more prominent cf. morphine) → can cause ↓ C.O. and ↓ BP
 - o Less ↓ BP cf. morphine due to ↓ histamine release
- (5) Respiratory effects:
 - o Potent and dose-dependent respiratory depression (↓ RR and ↓ TV) due to ↓ ventilatory responses to hypercapnoea/hypoxia
 - o Issues of persistent or recurrent respiratory depression post-operatively → due to 2° fentanyl peak a/w washout from pulmonary stores
 - o Chest and abdominal wall rigidity at high doses (2° to effect on GABA-ergic neurons) → difficulty delivering PPV
 - o Possesses anti-tussive effects
- (6) GI/GU effects:
 - o N/V → due to effects at CTZ
 - o Constipation → due to ↓ GI motility
 - o Spasm of sphincter of Oddi
 - o ↑ ureteric and bladder detrusor tone
- (7) ↓ histamine release → ↓ hypotension and bronchospasms
- (8) Others:
 - o No effect on ADH activity or immune cell function cf. morphine
 - o Dependence remains an issue
 - o Incompatible with STP → precipitates
 - o Cautious use in patients with hepatic impairment

Sufentanil:

Chemical structure: Synthetic opioid → phenylpiperidine derivative (thienyl analogue of fentanyl)

Mechanism of action: Highly selective μ opioid receptor agonist

Preparations: Clear, colourless solution (50 ug/mL) of sufentanil citrate for IV or epidural use

Clinical uses and doses:

- (1) Intra- and post-operative analgesia (IV 0.1-0.4 ug/kg or epidural 10-100 ug)
 - o 2000-4000x more potent cf. morphine, and 5-10x more potent cf. fentanyl
 - o Provides longer duration of analgesia and ↓ respiratory depression cf. fentanyl
- (2) Minimises haemodynamic responses to noxious surgical stimuli (IV 10-30 ug/kg) → not as reliable, and does not completely abolish catecholamine stress responses (even at high doses)
- (3) Induction and/or maintenance of GA (IV 20 ug/kg) → more rapid induction and faster emergence cf. high-doses fentanyl

Pharmacokinetics:

Absorption	Given via IV or epidural route only → onset of action in 1-6 mins, lasting 0.5-8 hrs
Distribution	- V_D 1.7-5 L/kg - Large protein binding (90%), esp to A1AGP - Weak base; pKa 8.0 → 20% unionised at physiological pH - ↑↑↑ lipid solubility (1700 octanol:H₂O coefficient) - Effect-site equilibration time ($t_{1/2\text{ keo}}$) = 6.2 mins → due to ↑ lipid solubility - Significant first-pass pulmonary uptake (60%; ≈ fentanyl) and uptake in adipose tissue → due to ↑ lipid solubility
Metabolism	Rapid hepatic metabolism via: - (i) N-dealkylation → nor-sufentanil (inactive metabolite) - (ii) O-demethylation → desmethyl-sufentanil (active metabolite with 10% activity) - Nb. ↑ HER → thus, clearance dependent on changes in HBF
Excretion	- Metabolites and small amounts (<1%) excreted unchanged in urine → ↑ lipid solubility allows for ↑ tubular reabsorption of free drug - Metabolites and free drug also excreted in bile - Clearance 10-20 mL/kg/min; Elimination $t_{1/2}$ 2-4.5 hrs - CSH_T (at 4 hrs) = 30 mins → small due to its relatively large V_D, such that ↓ plasma [] of drug is caused 1^oly by redistribution into inactive compartments in addition to metabolism/excretion

Pharmacodynamic effects (including issues and side-effects):

- (1) Analgesia → 2000-4000x more potent cf. morphine, and 5-10x more potent cf. fentanyl
- (2) MAC-sparing 60-70% with volatile-based anaesthesia
- (3) CNS effects:
 - o ↓ CMRO₂ and CBF
 - o EEG similar to fentanyl (initial ↓ β-activity and ↑ α-activity → α-activity disappears and δ-activity predominates)
 - o Myoclonus seizure-like activity (BUT no EEG spike-wave pattern) → but 1000x difference b/t analgesic dose and dose needed to produce seizures (cf. 160x fentanyl)
 - o Causes miosis (due to effects at Edinger-Westphal nucleus)
- (3) CVS effects
 - o Generally haemodynamically stable, but can cause ↓ HR, ↓ BP and ↓ C.O.
 - o Does not reliably blunt haemodynamic to noxious surgical stimuli, even at high doses
- (4) Respiratory effects:
 - o Potent and dose-dependent respiratory depression (↓ RR and ↓ TV) due to ↓ ventilatory responses to hypercapnoea/hypoxia
 - o Issues of persistent or recurrent delayed respiratory depression (like fentanyl)
 - o Chest and abdominal wall rigidity at high doses (2^o to effect on GABA-ergic neurons) → difficulty delivering PPV

- (5) GI effects → causes N/V (due to effects at CTZ)
- (6) Can cause histamine release → ↓ BP and bronchospasms
- (7) Used cautiously in patients with hepatic and renal failure

Alfentanil:

Chemical structure: Synthetic opioid → phenylpiperidine derivative (analogue of fentanyl)

Mechanism of action: Highly selective μ opioid receptor agonist

Preparations: Clear, colourless solution of alfentanil HCl (500 ug or 5 mg/mL) for IV use

Clinical uses and doses:

- (1) Short-term intra-operative analgesia (IV 5-25 ug/kg) → 5-10x less potent and 33% duration of action cf. fentanyl. Very rapid onset/offset of effects due to small $t_{1/2\text{ keo}}$
- (2) Reliably minimises haemodynamic responses and blunts catecholamine stress responses to noxious surgical stimuli and laryngoscopy (IV 15-30 ug/kg) → unlike sufentanil
- (3) Induction of GA (IV 150-300 ug/kg bolus → effect in 45 secs) and maintenance of GA (IVI at 25-150 ug/kg/hr) in conjunction with volatile agent
- (4) Maintain sedation in ICU → longer CSHT cf. sufentanil and remifentanyl but shorter cf. fentanyl and morphine

Pharmacokinetics:

Absorption	Given via IV route only → onset of action in 1.5 mins, lasting 5-10 mins
Distribution	- V_D 0.6 L/kg - Large protein binding (92%), esp to A1AGP - Weak base; pKa 6.5 → 89% unionised at physiological pH - ↑ lipid solubility (90 octanol:H₂O coefficient) - Moderate pulmonary first-pass uptake (only 10%) - Effect-site equilibration time ($t_{1/2\text{ keo}}$) = 1.4 mins → despite its ↓ lipid solubility, it has a very rapid onset of action (1.5 mins) is due to its ↓ pKa, which causes a ↑ unionised fraction at physiological pH (cf. fentanyl, which has a slower onset of action despite its ↑↑↑ lipid solubility. It has pKa 8.4, so only 9% unionised at physiological pH)
Metabolism	Hepatic metabolism via CYP3A4-mediated N-dealkylation at amide (produces N-phenyl-propionamide) and piperidine (produces norfentanyl) → metabolites are conjugated by glucuronidation Important to note → genetic polymorphism and drug-related inhibition/induction of CYP3A4 causes large interindividual variability in metabolism/clearance of alfentanil
Excretion	- Metabolites and unchanged drug (< 0.5%) are excreted in urine - Clearance 6 mL/kg/min - Elimination $t_{1/2}$ 1.5 hrs → despite small Cl, its small V_D allows for a short elimination $t_{1/2}$ (cf. fentanyl, which has a larger Cl but large V_D) - CSHT (at 4 hrs) = 60 mins → despite a shorter elimination $t_{1/2}$, alfentanil has a longer CSHT cf. sufentanil b/c it has a smaller V_D (I.e. ↓ redistribution of drug into inactive peripheral compartments)

Pharmacodynamic effects (including issues and side-effects):

- (1) Analgesia → 5-10x less potent cf. fentanyl
- (2) MAC-sparing with volatile-based anaesthesia
- (3) CNS effects:
 - Acute dystonia due to ↓ central DA neurotransmission

- Causes miosis (due to effects at Edinger-Westphal nucleus)
- (4) CVS effects:
 - Bradycardia and hypotension (but generally stable MAP and CO)
 - Reliably blunts haemodynamic responses to noxious surgical stimuli/laryngoscopy
- (5) Respiratory effects
 - Potent respiratory depressant ($\downarrow$ RR and $\downarrow$ TV) due to $\downarrow$ ventilatory responses to hypercapnoea/hypoxia $\rightarrow$ lacks delayed respiratory depression cf. fentanyl/sufentanil
 - Chest and abdominal wall rigidity at high doses (2° to effect on GABA-ergic neurons) $\rightarrow$ difficulty delivering PPV
- (6) GI effects:
 - $\uparrow$ biliary spasm due to $\uparrow$ contraction of sphincter of Oddi
 - $\downarrow$ N/V
- (7) Minimal histamine release
- (8) Used cautiously in patients with hepatic failure only (NOT renal failure)

Remifentanyl:

Chemical structure: Synthetic opioid $\rightarrow$ phenylpiperidine derivative of fentanyl with ester linkages

Mechanism of action: Pure μ opioid receptor agonist

Preparations: White crystalline powder of remifentanyl HCl (1,2,5 mg) with glycine buffer $\rightarrow$ diluted in N/S to produce a clear, colourless solution (stable for 24 hrs)

Important to note $\rightarrow$ Remifentanyl CANNOT be used neuraxially as it contains glycine (inhibitory NT in spinal cord)!!!

Clinical uses and doses:

- (1) Induction and maintenance of GA in conjunction with volatile/IV anaesthetic agent (IV 0.25-1 μ g/kg bolus over 60 secs, then infuse at 0.05-2 μ g/kg/min) $\rightarrow$ its pharmacokinetics allows for rapid onset and titratability of effects within 1-3 mins (due to $\downarrow$ $t_{1/2}$ keo) and rapid offset despite prolonged infusions (due to $\downarrow$ CSHT)
- (2) Intra-operative analgesia (same doses as above) $\rightarrow$ provides intense analgesia (with analgesic potency $\approx$ fentanyl), BUT additional post-operative analgesia required due to its short duration of action with cessation
- (3) Minimises haemodynamic responses and catecholamine stress responses to noxious surgical stimuli or intubation (same doses as above)
- (4) PCA (esp for labour/delivery)
- (5) Sedation (IV 0.05-0.1 μ g/kg/min) in conjunction with midazolam

Pharmacokinetics:

Absorption	Given via IV route only $\rightarrow$ onset of action in 1-2 mins
Distribution	- Small V_D (0.3 L/kg) - Large protein binding (70%), esp to A1AGP - Weak base; pKa 7.1 $\rightarrow$ 68% unionised at physiological pH - $\downarrow$ lipid solubility (20 octanol:H₂O coefficient) - Effect-site equilibration time ($t_{1/2}$ keo) = 1.1 mins $\rightarrow$ plasma [] reaches steady-state within 10 mins $\rightarrow$ rapid onset/offset and titratability
Metabolism	- Rapid metabolism by non-specific plasma and tissue esterases (via hydrolysis of ester linkages) $\rightarrow$ produces remifentanyl acid metabolite (1/4600th potent as parent compound $\rightarrow$ largely inactive) - Not metabolised by plasma cholinesterase (thus, not affected by plasma cholinesterase deficiency) and metabolised independent of liver or renal

	function Important to note → metabolism of remifentanyl by non-specific plasma and tissue esterases shows very little interindividual variability
Excretion	- Remifentanyl acid metabolite is excreted in urine - ↑ clearance (40 mL/kg/min) → due to rapid metabolism - ↓ elimination $t_{1/2}$ 3-10 mins - CSHT fixed at 4 mins regardless of duration of infusion → CSHT is insensitive to duration of infusion (cf. other opioids) due to its small V_D (I.e. ↓ distribution) and rapid clearance (I.e. ↑ metabolism) → thus, permitting rapid offset and easy titratability, even with prolonged infusions

Pharmacodynamic effects (including issues and side-effects):

- (1) Analgesia → similar potency as fentanyl BUT effects are short-lived only → long-acting opioid needs to be given to prevent unwanted pain following cessation of infusion
- (2) MAC-sparing with volatile based anaesthesia (by 50-90%)
- (3) CNS effects
 - o Sedation
 - o EEG effects → ↑ amplitude and ↓ frequency
 - o Seizure-like activity (like fentanyl/sufentanyl)
 - o Causes ↓ $CMRO_2$ and ↓ CBF at high doses
 - o Miosis (due to effects at Edinger-Westphal nucleus)
- (4) CVS effects
 - o Mild bradycardia (2° to direct vagal nuclei stimulation) → can lead to ↓ C.O. and ↓ BP
 - o Blunts haemodynamic responses to noxious surgical stimuli and laryngoscopy
- (5) Respiratory effects
 - o Respiratory depression (↓ MV 2° to ↓ RR and TV) due to central effects
 - o Chest and abdominal wall rigidity at high doses (2° to effect on GABA-ergic neurons) → difficulty delivering PPV
- (6) GI effects → ↓ N/V (due to its short duration of action)
- (7) Acute opioid tolerance due to high doses used intraoperatively (2° to effects on NMDA receptor) → produce post-operative hyperalgesia
- (8) No histamine release (I.e. minimal bronchospasm/↓ BP)

Methadone:

Chemical structure:

- Synthetic opioid
- Racemic → equal proportions of (l) and (d) enantiomers

Mechanism of action:

- (l)-methadone → potent opioid receptor agonist (μ receptor affinity > κ and δ receptor)
- (d)-methadone → NMDA receptor antagonist only

Note – Methadone is available either as (i) racemic mixture or (ii) (l)-enantiopure → racemic mixture has HALF opioid agonist potency (as (d)-enantiomer lacks opioid effects)

Clinical uses:

- (1) Analgesic → used to treat:
 - o (i) Chronic pain → highly effective oral agent due to its efficient absorption (↑ bioavailability), rapid onset of effect, prolonged duration of action (long $t_{1/2}$), and ↓ side-effects (esp sedation, abuse potential, tolerance/dependence and addiction)

- (ii) Neuropathic pain → due to its NMDA receptor antagonist effects
- (iii) Post-operative pain → IV 20 mg gives prolonged analgesia (> 24 hrs)
- (2) Suppress withdrawal symptoms in opioid-dependent patients
 - Highly effective oral agent due to efficient absorption, rapid onset of effect, and prolonged duration of action
 - Cf. to morphine, it is less sedating and its withdrawal is milder and less acute

Pharmacokinetics:

Absorption	PO – Well-absorbed in GIT (75% bioavailability 2° to ↓ hepatic FPM) IV
Distribution	90% protein binding; weak base
Metabolism	Hepatic metabolism → inactive metabolites
Excretion	Metabolites and unchanged drug (40%) excreted in urine and bile (Nb. ↑ urinary excretion with acidification of urine) Elimination t _{1/2} 18-36 hrs

Issues and side-effects:

- Side-effects are same as morphine (esp respiratory depression, constipation, biliary tract spasm) BUT ↓ sedation, miosis, euphoria/abuse potential, tolerance/dependence and addiction
- Drug half-life is very long and unpredictable → repeated drug dosing (esp as an analgesic) can cause significant accumulation and side-effects

Codeine:

Chemical structure:

- Naturally-occurring phenanthrene alkaloid
- Methymorphine → methyl substitution of OH group on 3-position of morphine

Mechanism of action:

- Codeine has very poor affinity for μ opioid receptor (I.e. analgesia, constipation, Etc), but high affinity for codeine receptor (I.e. antitussive)
- 10% of drug is O-demethylated by liver (CYP2D6) to morphine metabolite → potent μ opioid receptor agonist

Clinical uses:

- (1) Analgesia for mild-moderate pain only → b/c it is 10x ↓ potent cf. morphine
- (2) Anti-tussive agent
- (3) Anti-diarrhoeal agent

Preparations and doses:

- Oral tablet (15-60 mg) and syrup (5 mg/mL) and clear colourless solution of codeine phosphate (60 mg/mL) for parental use (IM/IV) → 30-60 mg (or 0.5-1 mg/kg in children)
- Tablet preparation often combined with a non-opioid analgesic (Eg. paracetamol, aspirin, ibuprofen)
- IV preparation should be avoided → due to histamine release causing hypotension

Pharmacokinetics:

Absorption	PO – Highly efficacious orally due to ↓ hepatic FPM (as a result of methylated 3-position of morphine) → this ↑ oral bioavailability (60-70%) IM (IV avoided due to ↓ BP)
Distribution	V _D 5.5 L/kg; 7% protein bound; weak base
Metabolism	Majority (90%) metabolised in liver via: - (i) Glucuronidation of OH group on 6-position (20%) →

	codeine-6-glucuronide - (ii) N-demethylation to norcodeine (20%) - (iii) O-demethylation by CYP2D6 (10%) to morphine → active metabolite with effects - (iv) Others (40%) to other metabolites (Eg. normorphine, Etc.)
Excretion	Metabolites and unchanged drug (10%) excreted in urine Clearance 100 L/hr; Elimination $t_{1/2}$ 3 hrs

Issues and side-effects:

- (1) Genetic polymorphism of CYP2D6 → 10% of Caucasians (or 30% HK Chinese) have genetic deficiency in CYP2D6 metabolism of codeine → do not produce morphine metabolite and thus lack adequate analgesia
- (2) Common side-effects are N/V, dizziness and constipation, but effects such as respiratory depression, physical dependence, sedation are less common (esp with oral preparation and at clinically appropriate dosages)
- (3) IV preparation causes significant ↓ BP 2° to histamine release → should be avoided

Oxycodone:

Chemistry: Semi-synthetic opioid

Mechanism of action: μ - and κ -receptor agonist

Clinical uses and preparations:

- Used to treat moderate to severe pain (acute or chronic) → analgesic effect is 1.5-2x ↑ potent cf. morphine
- Available as tablets (including sustained-release form “Oxy-contin”), suppository and solution for parental use

Pharmacokinetics:

Absorption	PO – Well-absorbed from GIT (oral bioavailability 60-90%) → onset of effects within 1 hr (3 hrs for sustained-release form) Can be given PR and parentally (SC/IM/IV) also
Distribution	- V_D 2.6 L/kg - 45% protein bound (α 1-acid glycoprotein) - Weak base (pKa 8.5) → 10% unionised at physiological pH - ↓ lipid solubility (0.7 octanol:H ₂ O coefficient)
Metabolism	Hepatic CYP450 metabolism to several metabolites (including oxymorphone, oxycodol, noroxycodone) → some are active
Excretion	Unchanged drug (20%) and metabolites excreted mainly in urine Clearance = 10 mL/min/kg; Elimination $t_{1/2}$ 3-4 hrs

Issues and side-effects:

- Generally better tolerated cf. morphine (due to ↓ respiratory depression, sedation, pruritis and N/V) BUT can still cause cardio-respiratory depression at high/toxic doses
- Main side-effects are constipation, fatigue, dizziness, memory loss, pruritis and N/V
- Can cause severe withdrawal symptom if withdrawn abruptly
- Genetic polymorphism → fast metabolisers have ↓ analgesic effect; slow metabolisers have ↑ toxicity
- Highly abused drug → crushed and solubilised for IV injection or intra-nasal use

Tramadol:

Chemical structure:

- Synthetic opioid → cyclohexanol derivative
- Racemic mixture → equal proportions of (+) and (-) enantiomers

Mechanism of action:

- Each enantiomer of racemic mixture has specific actions:
 - (+) enantiomer – Agonist at all opioid receptors (moderate μ -receptor affinity, weak κ - and δ -receptor affinity), inhibits 5-HT reuptake, and facilitates presynaptic 5-HT release
 - (-) enantiomer – Inhibits NAd reuptake

Important to note – Racemic mixture is SUPERIOR to an enantiopure preparation as isomers act synergistically towards its analgesic effects with minimal side-effects (I.e. ↓ respiratory depression, sedation, constipation, tolerance/dependence and abuse potential)

Preparations:

- All preparations are “racemic” → Tablets (50-400 mg) or clear colourless solution (50 mg/mL) for IV/IM

Clinical uses:

- (1) Analgesic agent (PO, IM, IV 1-2 mg/kg q6h)
 - Used to treat (i) moderate to severe pain (esp those who cannot take NSAIDs) and (ii) chronic pain
 - Acts as a centrally-acting analgesic agent → via opioid effects (see above) and 5-HT/NAd effects (enhances spinal descending inhibitory pathways)
- (2) Treat post-operative shivering (IM/IV 1 mg/kg)

Pharmacokinetics:

Absorption	PO – Well-absorbed from GIT (oral bioavailability 70%, but ↑ to 90% with repeated doses) Given IM and IV also
Distribution	V_D 4 L/kg; 20% protein binding
Metabolism	Hepatic CYP450 metabolism (via CYP2D6) via demethylation to several metabolites → O-desmethyl-tramadol is a major metabolite and only metabolite with analgesic activity. Metabolites are then glucuronidated for excretion
Excretion	Unchanged drug and metabolites excreted mainly in urine Clearance 7-10 mL/kg/min; Elimination $t_{1/2}$ 5-6 hrs

Effects:

- Similar effects as morphine EXCEPT:
 - (i) ↓ analgesic potency (by 5-10x)
 - (ii) ↓ respiratory depression, sedation, constipation and delay in gastric emptying at equi-analgesic doses
 - (iii) No clinically significant CVS effects (I.e. ↓ HR and BP)
 - (iv) Minimal tolerance, dependence or addiction
 - (v) Does not contract bile duct sphincter
 - (vi) Analgesic effect is only partly (30%) reversed by naloxone

Issues and side-effects:

- (1) Drug interactions
 - (i) TCAs and SSRI inhibit 5-HT/NAd reuptake also → can cause 5-HT syndrome (Eg. seizure, labile haemodynamics, coma, Etc.)
 - (ii) 5-HT₃R antagonists (Eg. ondansetron) → can interfere with 5-HT-mediated analgesic effects

- o (iii) Coumadin anticoagulants → ↑ bleeding risk
 - o (iv) Precipitates with midazolam
- (2) Should not be used in patients with epilepsy (due to seizure risk)
- (3) Emetogenic (↑ PONV)
- (4) ↑ volatile/MAC requirement → ↑ risk of awareness intra-operatively
- (5) Elimination $t_{1/2}$ ↑ with hepatic and renal impairment
- (6) CYP2D6 genetic polymorphism → 10% of population do not form active metabolite
→ ↓ analgesic effect

(IV) **Opioid Antagonist:**

Naloxone:

Chemical structure: Substituted oxymorphone derivative → N-alkyl group is substituted for N-methyl group on oxymorphone

Preparation: Clear colourless solution for IVI (400 mcg/mL)

Mechanism of action:

- Reversible (competitive) antagonist at all opioid receptors (μ , κ , δ receptors) → but highest affinity for μ receptor
- It binds to opioid receptor with high affinity → displaces opioid agonist from it but does not activate the receptor (I.e. lacks intrinsic activity)

Clinical uses:

- (1) Treat opioid-induced respiratory depression and sedation (esp post-operatively, a/w neuraxial opioids, or in neonates exposed to maternal opioids)
- (2) Treat opioid-induced pruritis and N/V (esp a/w neuraxial opioids)
- (3) Diagnose and treat suspected opioid overdose
- (4) Treat shock (only with doses > 1 mg/kg IV) → dose-related ↑ myocardial contractility not related to μ -receptor effect (? κ - or δ -mediated or non-opioid receptor mediated)

Doses:

- IV bolus 1-4 ug/kg for opioid overdose → onset of effect within 2 minutes 2° to its ↑ lipid solubility (I.e. crosses BBB rapidly)
- May need supplementary IV boluses or IV infusion (at 5 ug/kg/hr) when used to treat overdoses of longer acting opioids (esp morphine or high-doses of fentanyl) → b/c it has a short duration of action (30-45 mins) 2° to ↑ clearance rate and short elimination $t_{1/2}$

Note:

- Opioid-induced side-effects (Eg. respiratory depression, sedation, pruritis, N/V) → small incremental IV bolus doses given until desired end-point reached (I.e. reverse respiratory depression) without reversal of analgesia → generally 100-200 mcg needed
- Opioid overdose → generally 0.4-2 mg needed

Pharmacokinetics:

Absorption	PO – Well-absorbed from GIT (90%) but significant hepatic FPM (only 2% bioavailability) Parental (IV or IM)
Distribution	V_D 2 L/kg 45% protein binding (α 1-acid glycoprotein) pKa 8 (weak base) → 25% unionised at physiological pH Highly lipid soluble → easily crosses placenta
Metabolism	Hepatic metabolism by conjugation with glucuronic acid → forms naloxone-3-glucuronate
Excretion	Unchanged drug and metabolites excreted in urine ↑ clearance (25 mL/kg/min); short elimination ($t_{1/2}$ 60-90 mins)

Issues and side-effects:

- (1) Reversal of analgesia → thus, incremental IV bolus doses should be titrated to effect (I.e. reverse side-effect but maintaining analgesia)
- (2) CVS stimulation 2° to ↑ SNS activity caused by pain response a/w reversal of analgesia → can cause tachycardia, HTN, arrhythmias (incl VT/VF) and APO

- (3) Withdrawal syndrome in opioid-dependent patients → it can cross placenta can precipitate neonatal withdrawal in an opioid-dependent parturient
- (4) Antanalgesia in opioid naïve patients
- (5) N/V → esp if given quickly (< 2-3 mins) or high doses given
- (6) Drowsiness at excessive doses
- (7) ↑ MAC requirement → antagonises volatile-based GA

Naltrexone → reversible (competitive) antagonist at all opioid receptors (μ , κ , δ receptors) like naloxone, BUT it is highly effective orally and has sustained effects (> 24 hrs)

Nalmefene → 6-methylene analogue of naltrexone. Similar mechanism of action as naloxone and is equipotent to it, BUT has a longer duration of action 2° to its ↑ elimination $t_{1/2}$ of 10 hrs (esp useful to prevent delayed respiratory depression when treating ODs of long-acting opioids)

(V) Opioid Partial Agonists-Antagonists:

Important to note → Opioid partial agonists-antagonists can be used to (i) as analgesics or (ii) reverse opioid-induced respiratory depression → BUT NOT widely used due to mixed success and availability of pure opioid agonists and pure opioid antagonists

Buprenorphine:

- Structurally similar to morphine
- Mechanism of action – Partial agonist on μ and NOP opioid receptors
- Effects – More potent than morphine and with $\uparrow$ duration of action (~ 10 hrs) due to $\uparrow$ receptor binding → causes analgesia at $\downarrow$ doses (μ receptor effect) but at $\uparrow$ doses causes anti-analgesic effects (NOP receptor effect). Associated with severe and prolonged N/V

Nalorphine:

- Mechanism of action – κ -receptor agonist and μ -receptor antagonist
- Effects – Used as antagonist to morphine previously, but found to have analgesic effect. Withdrawn from use 2° to $\uparrow$ incidence of psychomimetic effects at analgesic doses

Pentazocine:

- Mechanism of action – Partial agonist on κ - and δ -receptors, but antagonist at μ -receptor
- Effects – Analgesia with minimal respiratory depression; BUT $\uparrow$ incidence of N/V, hallucinations and dysphoria → thus, rarely used

Nalbuphine:

- Mechanism – Partial κ -receptor agonist and partial μ -receptor antagonist
- Effects – Equipotent to morphine but ceiling effect with respiratory depression and analgesic actions → thus, limited use

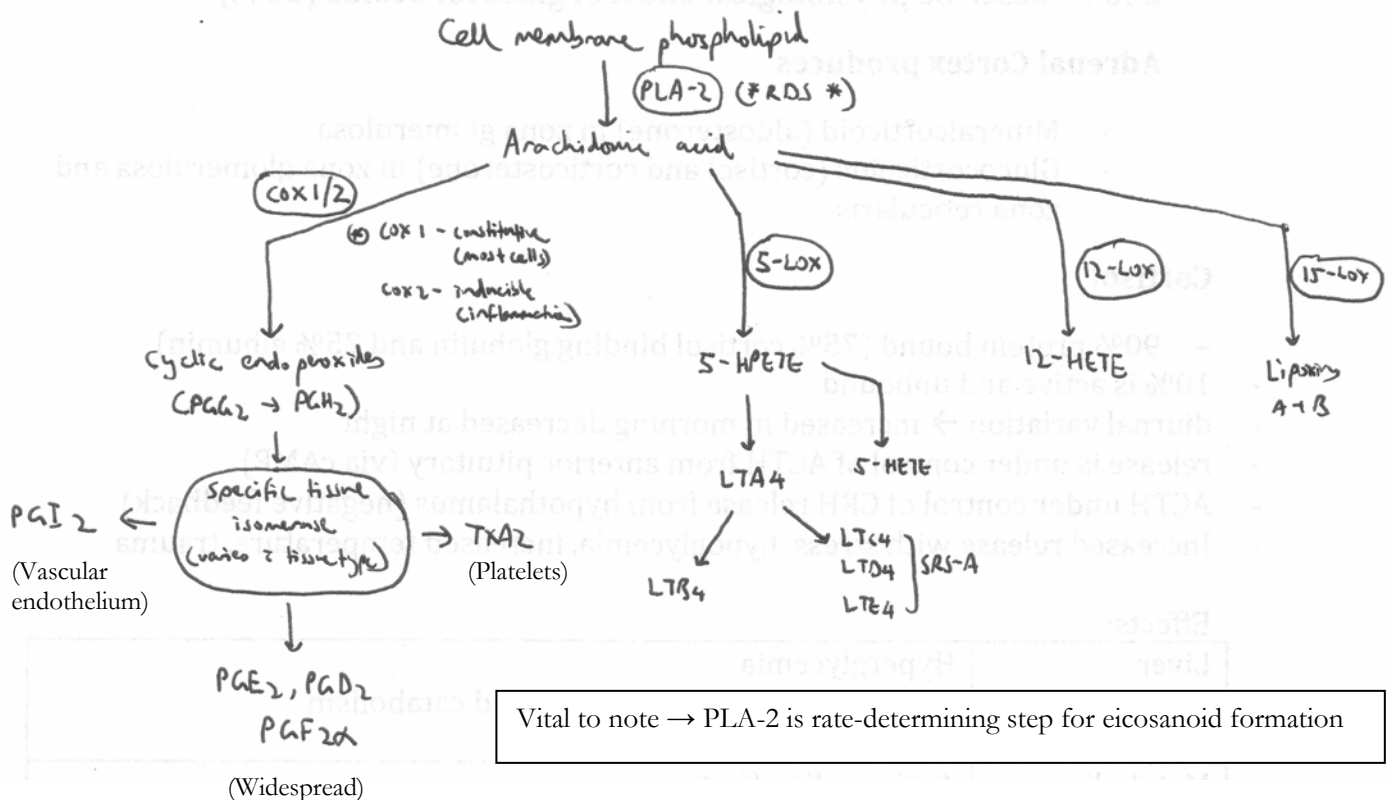
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

(a) *To describe the eicosanoid pathway and the physiological role of prostaglandins.*

Eicosanoids:

- Diverse group of molecules generated de novo from arachidonic acid → a 20-C polyunsaturated FA (with 4 double-bonds) found in cell membrane phospholipids
- Includes – (i) Prostaglandins, (ii) Thromboxanes, (iii) Leukotrienes, (iv) Lipoxins, and (v) other related molecules (Eg. PAF, 5-HE_{TE}, 12-HE_{TE}, Etc.)
- Produced by all cells in body (esp kidney, heart, lungs, liver, pancreas, brain, reproductive organs) EXCEPT RBC → specific eicosanoids are made by various tissues (Ie. not all cells produce same type) → this is dictated by type of enzymes expressed by cells in tissue
- Synthesised in small quantities prior to release (NOT stored preformed in tissues) → exert 1^oly local paracrine effects → very potent activity → but rapidly inactivated (within seconds-minutes)

Formation of eicosanoids:



Prostaglandins:

- Synthesis:
 - o Arachidonic acid → converted to cyclic endoperoxides (PGG₂ → PGH₂) via COX (cyclooxygenase) → this enzyme has 2 isoforms:
 - COX 1 is “constitutive” → expressed in most cells (esp gastric mucosa, renal parenchyma, platelets) → produce PGs involved in maintaining homeostasis (Ie. platelet aggregation, gastric barrier, renal function)
 - COX 2 is “inducible” → expressed in sites of tissue injury → produce PGs involved in inflammatory response, pain, pyrexia and carcinogenesis

Note – COX3 is a variant of COX-1 that exists centrally → mediates antipyrexial and analgesic properties of paracetamol

- o PGG₂/PGH₂ → converted by various tissue isomerases into:

- (i) PGI-2
- (ii) PGD-2
- (iii) PGE-2
- (iv) PGF2 α
- (v) TXA2

Note – Specific GPCR exists for each PG type (DP, FP, IP, TP, EP receptors)

Note – Different PGs are produced in different tissue types (Eg. TXA2 in platelets, PGI2 in vascular endothelium, Etc.)

- Catabolism → rapid (< 1 mins)
 - Locally, PG are taken-up → degraded intracellularly by PG-specific enzymes
 - Also extensive 1st pass metabolism in lungs → ↑ [] of PG-specific enzymes
- Effects:

CVS	Vascular SM relaxation → PGD2, PGE2, PGI2 Vascular SM contraction → TXA2
Respiratory	Bronchial SM relaxation → PGE2 Bronchial SM contraction → PGE2, PGF2 α , TXA2
GIT	GI SM relaxation → PGD2, PGE2 GI SM contraction → PGE2 Gastroprotective effects (↑ gastric mucous secretion and ↓ acid secretion) → PGE2, PGI2
Renal	Regulates renal haemodynamics, RAAS, glomerulotubular function (Na ⁺ /H ₂ O excretion) → PGE2, PGI2
Haemostasis	Platelet aggregation (and vasoconstriction) → TXA2 Inhibition of platelet aggregation (and vasodilation) → PGI2
Inflammation, pain and fever	PGD2, PGE2, PGF2 α , PGI2 → (i) ↑ local tissue blood flow → oedema, (ii) sensitises afferent nerve endings to pain stimuli; also cause fever centrally
Reproduction	Male → PG important in semen Female → uterine relaxation (PGD2), uterine contraction (PGE2, PGF2 α) → vital during parturition

Leukotrienes:

- Synthesis:
 - Arachidonic acid → converted to 5-HPETE via 5-LOX (lipoxygenase) → then converted to LTA 4
 - LTA converted either to → (i) LTB4, or (ii) Slow-reacting substances of anaphylaxis (SRS-A) – LTC4, LTD4, LTE4
 - LTs are produced in in lungs, platelets, mast cells, WBC
- Effects:

CVS	Vascular SM relaxation (except for coronaries – causes contraction) → LTC4, LTD4, LTE4
Respiratory	Bronchial SM contraction → LTC4, LTD4, LTE4
Inflammation/pain	Chemotaxis → LTB4

(b) *To classify the non-steroidal anti-inflammatory drugs.*

NSAIDs → group of drugs with analgesic, anti-inflammatory and antipyretic effects

Classification of NSAIDs:

Non-specific COX inhibitors	- Salicylates (aspirin) - Acetic acid derivatives (diclofenac, ketorolac, indomethacin) - Propionic acids (ibuprofen, naproxen) - Oxicams (piroxicam, tenoxicam) - Pyrazolones (phenylbutazone) - Anthralinic acids (mefenamic acid) - Para-aminophenols (paracetamol)
Preferential COX-2 inhibitors	- Oxicams (meloxicam)
Specific COX-2 inhibitors	- Pyrazoles (parecoxib, celecoxib, rofecoxib) - Methsulphone (etoricoxib) - Phenylacetic acid derivative (lumiracoxib)

Clinical uses of NSAIDs:

- (1) Analgesia:
 - o Treat mild to moderate pain (esp useful when a/w inflammatory conditions, such as OA, RA, gout, Etc.)
 - o Treat post-operative pain (esp useful in reducing opioid use → acts synergistically with opioids)
- (2) Anti-inflammatory effects (Eg. OA, RA, gout, ankylosing spondylitis, Etc.)
- (3) Anti-pyretic effects
- (4) Others → anti-platelet effects (low-dose aspirin) and closure of PDA (indomethacin)

Important to note → All NSAIDs have “ceiling effects” with regards to their clinical uses, and ↑↑↑ dose to attempt to achieve a greater effect only increases risk of drug-induced toxicity!!!!

Important to note → Benefits of NSAIDs (cf. opioids):

- (i) Anti-inflammatory and anti-pyretic response
- (ii) Immediate and pre-emptive analgesia (due to ↓ activation and sensitisation of peripheral nociceptors) → also synergistic analgesic effects with opioids
- (iii) Longer duration of action
- (iv) ↓ dose variability
- (v) Absence of dependence/tolerance (Ie. no addiction potential), respiratory depression, cognitive effects, pupillary changes, biliary spasms and pruritis
- (vi) ↓ N/V

Mechanism of action of NSAIDs:

- NSAIDs inhibit COX enzyme reversibly (EXCEPT aspirin – see below) → ↓ PG and TX synthesis from cell membrane → resulting in:
 - o (i) Anti-inflammatory effects (↓ PGE2, PGF2α)
 - o (ii) Analgesic effects (↓ PGD2, PGE2, PGF2α, PGI2)
 - o (iii) Antipyretic effects (↓ PGs centrally)
 - o (iv) Bleeding 2° to anti-platelet effects (↓ TXA2)
 - o (v) Gastric mucosal ulceration 2° to ↓ protective gastric barrier (↓ PGE2, PGI2)
 - o (v) Renal dysfunction 2° to ↓ RBF (↓ PGE2, PGI2)
- NSAIDs can either inhibit (i) COX-1 and -2 non-specifically or (ii) COX-2 specifically:

- o COX-1 inhibition → responsible for many adverse effects a/w NSAIDs b/c it disrupts physiological functions of PGs synthesised by COX-1 (Ie. renal impairment, bleeding, PUD, Etc.)
- o COX-2 inhibition → improve side-effect profile of NSAID by specifically disrupting the pathophysiological functions of PGs synthesised by COX-2 (Ie. anti-inflammatory, analgesia, antipyresis, Etc.)

Pharmacokinetics of NSAIDs:

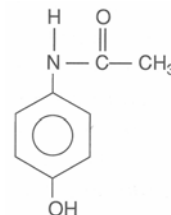
Absorption	- PO – Well absorbed in GIT (esp in small bowel), ↓ first pass metabolism - PR - Some IV (only parecoxib, ketorlac, diclofenac)
Distribution	- ↑ plasma protein bound (> 95%), EXCEPT paracetamol (10%) → this means their effects are potentiated if other highly protein bound drugs (Eg. warfarin) displaces them - ↓ V_D (EXCEPT paracetamol) - Lipid-soluble NSAIDs cross BBB → CNS effects (Δ mood/cognition) - Ionisation – Weak acid (pKa 3-5) → mainly ionised at physiological pH
Metabolism	Most are metabolised by liver → some have active metabolites (Eg. paracetamol, aspirin, parecoxib, Etc.)
Excretion	Inactive metabolites (and some unchanged drug) are excreted in urine and bile in varying amounts

(c) *To describe the pharmacology of paracetamol and its toxicity.*

Paracetamol:

Class – Non-specific COXi → Para-aminophenol

Effects – Moderate analgesic and antipyretic effects, BUT lacks significant antiinflammatory effect



Clinical use:

- It is used as an analgesic and/or antipyretic agent in patients who cannot take aspirin and NSAID for those effects (esp paediatric patients, patients with PUD, renal dysfunction or coagulopathy) → this is b/c paracetamol does NOT:
 - o (i) Cause gastric irritation and PUD
 - o (ii) Alter platelet function
 - o (iii) Cause Reye's syndrome in children
 - o (iv) Cause renal dysfunction to the same extent as NSAIDs/aspirin
- Dose – 4 g/day in divided dose (in children → 10-15 mg/kg q4h up to 90 mg/kg/day)
- Presentation – PO 500 mg tablet (+/- combination with opioid; Eg. codeine) or 120 mg/5 mL elixir; PR 125 mg or 1g suppository; IV 1 g in 100 mL (contains mannitol as solubilising agent)

Mechanism of action:

- Inhibits COX3 (COX-1 variant) in CNS → ↓ PG centrally → produces analgesic and antipyretic effects
- Note – Minimal anti-inflammatory effects are due to its modest peripheral COX inhibition of PG synthesis

Pharmacokinetics:

Absorption	- PO: Well-absorbed from small intestines with oral bioavailability 80% - Also can be given PR and IV
Distribution	- Low protein-binding (10%) - Large V_D
Metabolism	- Hepatic metabolism – 2 paths: - 80% – Via hydroxylation → then conjugation to glucuronide (also sulphate and cysteine) into inactive metabolites - 10% – A highly toxic metabolite is produced (N-acetyl-p-amino-benzoquinoneimine) in small amounts at therapeutic doses, but is rapidly conjugated with glutathione into a non-toxic metabolite
Excretion	- Metabolites are excreted in urine; small fraction is excreted unchanged - Elimination $t_{1/2} \sim 2$ hrs

Toxicity:

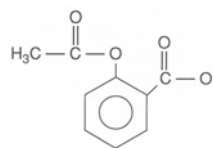
- (1) Hepatotoxicity
 - o Toxic daily dose > 4-6 g (while lethal dose occurs at > 10-15 g (or > 300 mg/kg LBM)) → but the toxic and lethal doses are lower in “at-risk” groups:
 - (i) EtOH abuse (due to CYP450 induction (↑ toxic metabolite produced) and ↓ glutathione stores)
 - (ii) Malnutrition (due to ↓ glutathione stores)
 - (iii) Elderly (due to ↓ glutathione stores)
 - (iv) Preexisting liver dysfunction
 - o Mechanism:
 - At therapeutic doses – “N-acetyl-p-amino-benzoquinoneimine” (highly toxic metabolite) is produced in small amounts, but is rapidly conjugated with hepatic glutathione (anti-oxidant) into a harmless metabolite

- BUT with toxic doses – Hepatic conjugation pathway is saturated and ↑↑↑ N-acetyl-p-amino-benzoquinoneimine is produced → this depletes hepatic glutathione stores, causing remaining N-acetyl-p-amino-benzoquinoneimine to then forms covalent bonds with sulphhydryl groups on hepatocytes → results in centrilobular hepatic necrosis
- Clinical features:
 - Generally conscious and c/o N/V, epigastric pain, erythema, sweating → later developing:
 - Acute haemolytic anaemia
 - Develop hepatic failure (I.e. jaundice and cholestasis) after 48 hrs
 - LFT/INR derangements at 3-5 days
 - Fulminant hepatic failure at 3-7 days
 - With severe OD, can present with hypotension/shock
- Diagnosis – Serum paracetamol levels → correlate with “nomogram” to predict likelihood of liver damage → used as a guide to dictate therapy
- Treatment:
 - (i) Activated charcoal/gastric lavage → limit paracetamol absorption
 - (ii) Replace hepatic glutathione store within 12 hrs of OD → permits glucuronidation of toxic metabolite
 - (a) Oral methionine → ↑ glutathione synthesis
 - (b) IV N-acetylcysteine → hydrolysed to cysteine (which is a glutathione precursor)
 - Nb. IV NAC is preferred b/c of N/V a/w toxicity (I.e. ↓ oral methionine absorption)
 - (iii) IV glucose → due to risk of ↓ BGL with liver dysfunction
 - (iv) Serial monitoring of LFTs and coagulation studies
 - (v) Referral to a specialist centre
- (2) Analgesic-induced nephropathy
 - Paracetamol metabolites (esp p-aminophenol) concentrate in hypertonic renal papillae → they are oxidised into metabolites that form covalent bonds with sulphhydryl groups on tissues → cause papillary necrosis
- (3) Others – Skin rash, allergic reactions

(d) *To describe the pharmacology of aspirin and its adverse effects.*

Aspirin:

Class – Non-specific COX_i → Salicylates



Effects – Analgesic, antipyretic, anti-inflammatory and anti-platelet effects

Clinical uses:

- It is used as an – (i) Analgesic (for mild-moderate pain), (ii) Antipyretic, (iii) Anti-inflammatory agent (Eg. for RA, OA), and (iv) Anti-platelet agent to treat or prevent arterial thromboembolism (Ie. treat ACS, prevent CVAs, prevent vascular stent/graft thrombosis)
- Dose – Loading dose of PO 300 mg, then 75-100 mg daily
- Presentation – PO as tablet (75-600 mg) or effervescent

Mechanism of action:

- Aspirin irreversibly acetylates COX enzyme → ↓ synthesis of PGs and TXA₂ → anti-platelet, analgesic, anti-pyretic and anti-inflammatory effects

Important to note → Low dose aspirin is used to treat or prevent arterial thromboembolism b/c it inhibits platelet COX-1 → ↓ TXA₂ production → ↓ platelet aggregation and vasoconstriction. This effect lasts 10-14 days (cf. other NSAIDs, which is brief) b/c (i) COX inhibition by aspirin is irreversible and (ii) platelets cannot regenerate new COX enzyme (as it lacks nuclei), thus new platelets need to be produced

- Its metabolite (salicylate) is active and also inhibits COX enzyme → but via a non-acetylating mechanism

Pharmacokinetics:

Absorption	- Given PO → rapidly absorbed within GIT, esp small intestine > stomach b/c: - Aspirin is a weak acid (pK_a 3) → ↑ unionised fraction in acidic gastric juice → but absorption in stomach limited by alkaline gastric mucosal lining (Ie. salicylate ions trapped and unable to reach systemic circulation) - Small bowel absorptive area is much larger than stomach - Rate of absorption depends on: - (i) pH of GI tract → ↑ alkalinity causes ↑ ionised fraction → ↓ absorption - (ii) Presence of food → ↓ absorption - (iii) Preparation → effervescent has ↑ absorption cf. tablet
Distribution	- High protein-binding (85%), esp to albumin - Low V_D
Metabolism	- Rapid hydrolysis by intestinal and hepatic esterases to salicylate (active metabolite) - Salicylate is then conjugated to glycine in liver → forms salicyluric acid
Excretion	- Aspirin and its metabolites are excreted in urine → urinary excretion is enhanced under alkaline conditions 2° to “ion trapping” in urine (Ie. use IV NaHCO₃ to treat overdose) - Elimination t_{1/2} of aspirin is 15 mins, while salicylate is 2-3 hrs (BUT can be variable b/c glycine conjugation of salicylate can be saturated with overdose → follows “zero-order kinetics”)

Side-effects:

- (1) GI toxicity (most common)
 - o Salicylate ions are trapped in alkaline environment of gastric mucosal cell → inhibit gastric mucosal COX-1 → ↓ PGE₂/PGI₂, which are implicated in GI mucosal protection (I.e. mucous secretion, HCO₃ secretion, blood supply) against gastric acid/enzyme attack → GI toxicity (esp gastritis, gastro-duodenal ulcers, Fe-deficiency anaemia and GI bleeding)
 - o GI toxicity is dose-related (but even low doses can cause GI bleeding), but can be ↓ with enteric-coated formulations
- (2) Prolonged bleeding time
 - o Manifests as easy bruising, GI bleeding (melaena), epistaxis
 - o Mechanism:
 - At low doses, aspirin causes prolonged platelet dysfunction – It irreversibly acetylates platelet COX-1 → ↓ TXA₂ → ↓ platelet aggregation and vasoconstriction. Thus, need to wait 10-14 days for platelets to regenerate with new COX-1
 - At large doses chronically, aspirin inhibits prothrombin synthesis
 - o Should be withheld 7 days prior to invasive surgery due to risk of ↑ bleeding (but normally prolonged bleed time dissipates within 48 hrs of cessation)
- (3) Aspirin-induced asthma
 - o Occurs in 10-20% of asthmatics (esp those with chronic rhinosinusitis, nasal polyps or middle-aged)
 - o Aspirin inhibits COX-mediated conversion of AA to anti-inflammatory PG (esp PGE₂) → instead more AA is converted by LOX to LTs, which are pro-inflammatory and cause bronchoconstriction
 - o May develop cross-sensitivity with other NSAIDs also
- (4) Hepatic dysfunction → elevated transaminases (often due to reversible hepatic damage), but in severe cases can be a/w fatty infiltration
- (5) Renal dysfunction
 - o Chronic low-dose aspirin (I.e. below anti-inflammatory range) has minimal effects on renal PG synthesis → unlikely to cause renal dysfunction
 - o Aspirin can also cause “analgesic nephropathy” → papillary necrosis and interstitial fibrosis
- (6) Reye’s syndrome:
 - o Aspirin causes widespread mitochondrial damage, fatty changes in liver (causing hepatic failure), and encephalopathy a/w cerebral oedema → 40% mortality rate
 - o Mainly seen in children (uncommon in adults) → thus, aspirin is only indicated for children < 12 y.o. in certain conditions (I.e. juvenile RA or Still’s disease)
- (7) Obstetric issues → aspirin prolongs labour and ↑ PPH risk (due to loss of uterotonic effects and platelet dysfunction)
- (8) Allergy reactions → rare

Toxicity with overdose:

- Clinical features:
 - o Conscious (unless with massive OD)
 - o Tinnitus → an early sign of OD
 - o Pyrexia and sweating
 - o Blurred vision
 - o Tachycardia
 - o Hyperventilation
 - o Respiratory alkalosis (later complicated by metabolic acidosis)
 - o Hyperglycaemia
- Pathophysiology:

- Aspirin uncouples [O] phosphorylation → ↑ O₂ consumption and CO₂ production → hypermetabolic state (I.e. ↑ BGL, hyperthermia, hyperventilation, ↑ HR, Etc.)
- Respiratory alkalosis occurs due to hyperventilation → caused by (i) direct aspirin stimulation of medullary ventilatory centres and (ii) hypermetabolic state
- In late stages, mixed respiratory and metabolic acidosis occur → due to (i) respiratory depression 2° to aspirin and (ii) accumulation of metabolic acids 2° to renal dysfunction (I.e. accumulate strong acids) and ↑ CHO metabolism (I.e. lactic acid)

Note – Mixed respiratory/metabolic acidosis occurs 1°ly in children → rare in adults

- Treatment:

- (1) Activated charcoal/gastric lavage → ↓ aspirin absorption
- (2) Forced-alkaline diuresis (diuretic + IV NaHCO₃)
 - (i) Treat metabolic acidosis → ↓ transfer of salicylate from plasma to CNS
 - (ii) ↑ trapping of salicylate within renal tubule → ↑ urinary excretion
- (3) Haemofiltration/haemodialysis

(e) *To outline the pharmacology of the non-selective COX inhibitors.*

(I) Acetic acid derivatives:

(1) *Diclofenac:*

- Effective analgesic, anti-inflammatory and anti-pyretic agent that can be given parentally and is a/w ↓ GI toxicity cf. other NSAIDs (esp aspirin and indomethacin)
- Available PO, PR and parentally (IM/IV) → oral form can be provided in combination with “misoprostil” as prophylaxis against GI toxicity. Given up to 150 mg/day in divided doses (1 mg/kg tds for children)
- Pharmacokinetics – Well absorbed in GIT. 99% protein bound with small V_D (0.15 L/kg). Metabolised in liver (via hydroxylation and conjugation) into inactive metabolites that are excreted in urine (60%) and bile (40%). < 1% excreted unchanged in urine. Elimination $t_{1/2}$ 1-2 hrs
- Issues:
 - Parental form needs to be diluted and given slowly (over 30 mins) as it is highly irritant → cause thrombosis with IVI, or severe pain and myositis with IMI
 - Causes ↑ plasma levels of digoxin and lithium (but not warfarin or oral hypoglycaemics) due to competition with plasma protein binding

(2) *Ketorolac:*

- Potent analgesic and antipyretic (but limited anti-inflammatory effect)
- Available PO and parentally (IM/IV) → max 40 mg daily dose
- Parental form has onset within 1 hr and effects last up to 6 hrs → useful for post-operative analgesia
- Pharmacokinetics – 99% protein binding. Hepatic metabolism to inactive metabolites. Elimination $t_{1/2}$ 5 hrs

(3) *Indomethacin:*

- Most potent COX inhibitor with significant anti-inflammatory effects (but less effective analgesic and antipyretic effects) → mainly used to treat inflammatory disorders (Eg. ankylosing spondylitis, acute gout, Etc.) and promote closure of ductus arteriosus in premature infants
- Available PO and PR
- Drug use limited by its side-effects → mainly GI disturbances, severe headaches, and hepatic dysfunction (and other NSAID-related adverse effects)
- Pharmacokinetics – Well-absorbed in GIT (80% oral bioavailability). 99% protein bound. Hepatic metabolism to inactive metabolites excreted in urine/bile (5% excreted unchanged). Elimination $t_{1/2}$ 6 hrs

(II) Propionic acids:

(1) *Ibuprofen:*

- Provides mild analgesic, anti-inflammatory and anti-pyretic effects only → BUT has the lowest incidence of NSAID-related side-effects (esp GI toxicity and drug interactions) → hence, it is the most commonly used NSAID!
- Available as tablet (200-600 mg) and elixir (20 mg/mL) → max 1.5 g/day in adults (20 mg/kg/day in divided doses in children, BUT not be used in children < 1 y.o.)
- Pharmacokinetics – Well-absorbed orally. 99% protein binding. Hepatic metabolism (via hydroxylation and carboxylation) to metabolites that are excreted in urine (< 1% excreted unchanged in urine). Elimination $t_{1/2}$ 2-3 hrs

(2) *Naproxen:*

- Long elimination $t_{1/2}$ → allows bd administration
- Metabolised by hepatic dealkylation (via CYP450) with < 10% excreted unchanged in urine

(III) Pyrazolones:

Phenylbutazone:

- Potent anti-inflammatory agent whose use is severely limited by its side-effects:
 - o Given as a short-course (< 7 days) for inflammatory conditions (esp ankylosing spondylitis, RA and gout) → not routinely used for analgesia or anti-pyresis
 - o Main side-effects are haematological (agranulocytosis and aplastic anaemia), but also include GI disturbances (N/V, abdominal pain, hepatic dysfunction), Na^+ /H₂O retention, allergic rash, and drug displacement (esp warfarin, aspirin, sulphonamides, oral hypoglycaemics)
- Pharmacokinetics – Well absorbed in GIT. 98% protein binding. Metabolised in liver by hydroxylation to active metabolite (oxyphenbutazone) with same activity as parent drug → then glucuronidated to inactive metabolite that is excreted slowly in urine. Elimination $t_{1/2}$ 50-100 hrs

(IV) Oxicams:

(1) *Tenoxicam*:

- Useful for peri-operative analgesia b/c it is available parentally (IV dosing gives rapid onset of action) and has a long elimination $t_{1/2}$ = 72 hrs (allows daily dosing) → BUT use limited by significant side-effects!
- Pharmacokinetics – Well absorbed from GIT (high oral bioavailability). 99% protein bound. Hepatic metabolism to inactive metabolites excreted in urine (66%) and bile (33%)

(2) *Meloxicam*:

- Available as a tablet and suppository (max 15 mg/day dose)
- Selective for COX-2 (up to 50x potent against it cf. COX-1) → hence, ↓ GI toxicity (cf. other NSAIDs) at 7.5 mg/day dosing
- Pharmacokinetics – Slowly but completely absorbed from GI (oral bioavailability 90%). 99% protein bound (to albumin). Hepatic metabolism to inactive metabolites that are excreted in urine and bile (3% unchanged in urine). Elimination $t_{1/2}$ 20 hrs

(f) *To outline the pharmacology of the selective COX 2 inhibitors.*

Clinical features of COX-2 selective inhibitors (cf. non-selective NSAIDs):

- (i) Similar analgesic, anti-inflammatory and anti-pyretic effects
- (ii) Similar degree of renal dysfunction
- (iii) ↓ bleeding risk (as they do not inhibit platelet function)
- (iv) ↓ GI toxicity side effects
- (v) ↓ incidence of bronchospasm in asthmatics
- (vi) ↑ pro-thrombotic tendency (see below)

Important to note – Chronic therapy (> 12 months) with COX-2 selective inhibitors have equivalent rates of GI toxicity and other toxic effect (Eg. HTN, CCF, hepatotoxicity) as non-COX specific NSAIDs, BUT also have ↑ risk of CVA/MI → thus they are contraindicated in patients with IHD, PVD, CVD and mild CCF

(I) Pyrazoles:

(1) *Parecoxib:*

- Acts as a “prodrug” → inactive on its own, but is converted to an active drug (valdecoxib) by hepatic metabolism via amide hydrolysis

Note – Elimination $t_{1/2}$ of “inactive” parecoxib is 45 mins, while that of “active” valdecoxib is 8 hrs!

- ONLY COX-2 selective inhibitor that can be given parentally
- Useful for post-operative analgesia → presented as a powder that needs to be reconstituted in N/S → IV or IM 40 mg, then 20-40 mg q6-12 hrly (max 80 mg/day)
- Due to its short-term use (cf. valdecoxib) → it is NOT associated with adverse dermatological hypersensitivity reactions (see below)

(2) *Valdecoxib:*

- COX-1:COX-2 ratio of 1:60
- Available orally only for arthritic conditions
- Pharmacokinetics – Metabolised via hydroxylation to 1-OH-valdecoxib by hepatic CYP3A4 and 2C9 → then glucuronidated and renally excreted. Elimination $t_{1/2}$ 8 hrs

Note:

- Metabolism is affected by CYP2C9 inducers (Eg. carbamazepine) and inhibitors (Eg. omeprazole, fluconazole)
- Its metabolism inhibits other CYP450-mediated drug metabolism → CYP2C9 (Eg. omeprazole, phenytoin, diazepam) and CYP2D6 (Eg. propranolol, flecainide)

- Possesses a sulphonamide group → contraindicated in those with sulphonamide allergy due to risk of severe hypersensitivity reactions (Stevens-Johnson syndrome, toxic dermal necrolysis, exfoliative dermatitis, angio-oedema)

(3) *Celecoxib:*

- COX-1:COX-2 ratio of 1:30
- Available orally only → PO 100 mg tablets (max 200 mg bd) for arthritic conditions
- Pharmacokinetics – Well absorbed orally (with peak plasma [] at 2-3 hrs). Hepatic metabolism by CYP2C9 to inactive metabolites (Note – metabolism affected by CYP2C9 inducers and inhibitors – see above). Metabolites and small amounts of unchanged drug are excreted in urine. Elimination $t_{1/2}$ 8-12 hrs
- Possesses sulphonamide group → contraindicated with sulphonamide allergy

(4) *Rofecoxib*:

- Withdrawn in 2004 due to ↑ MI risk

(II) Methysulphone:

- *Etoricoxib*
 - o COX-1:COX-2 ratio of 1:345
 - o Available orally only. Has a predictable side-effect profile

(III) Phenylacetic acid derivative:

- *Lumiracoxib*
 - o COX-1:COX-2 ratio of 1:700
 - o Available orally only. Main issue is serious hepatotoxicity → contraindicated with liver disease (including any LFT derangements). Needs constant LFT monitoring

(g) *To describe the adverse effects of the NSAIDs.*

(1) GI toxicity:

- Within GI tract, COX-1 synthesises PGE₂/PGI₂ which are implicated in GI mucosal protection (I.e. mucous secretion, HCO₃ secretion, blood supply) against gastric acid/enzyme attack
- NSAIDs inhibit GIT COX-1 → ↓ PGE₂/PGI₂ → ↑ risk of GI toxicity (esp gastritis, gastro-duodenal ulcers, Fe-deficiency anaemia and GI bleeding)

Note – Aspirin causes ↑ GI toxicity as salicylate ions are trapped within alkaline gastric mucosa lining → ↑ effect on gastric COX

- GI toxicity may be ↓ with use of:
 - (i) Concurrent H₂RB, PPI, misoprostol
 - (ii) COX-2 selective inhibitors or paracetamol as an alternate

(2) NSAID-sensitive asthma:

- NSAIDs inhibit COX-mediated conversion of AA to anti-inflammatory PG (esp PGE₂) → instead more AA is converted by LOX to LTs, which are pro-inflammatory and cause bronchoconstriction
- Occurs in 10-20% of asthmatics (esp those with chronic rhinosinusitis, nasal polyps or middle-aged) → dose-dependent sensitivity to aspirin and non-selective NSAIDs
- NSAID-sensitive asthma may be ↓ with use of COX-2 selective inhibitors or paracetamol

(3) Renal dysfunction:

- PGE₂ and PGI₂ synthesised by renal COX are vital in autoregulation of RBF/GFR (esp when circulating vasoconstrictors are high (Eg. Ang II, NAd))
- NSAIDs ↓ PG synthesis → cause pre-renal azotemia and renal medullary ischaemia 2° to ↓ renal perfusion → ARF
- This occurs with non-selective NSAIDs and COX-2 selective inhibitors (esp in the presence of risk factors – hypovolaemia, underlying renal disease, use of nephrotoxic agents (Eg. ACEi, contrast, aminoglycosides), DM, CCF, sepsis)

Note:

- Chronic low-dose aspirin has minimal effects on renal PG synthesis → unlikely to cause renal dysfunction
- “Analgesic nephropathy” can occur with aspirin and paracetamol use (see above)

(4) Bleeding:

- Platelets contain COX-1 only, which synthesises TXA₂ → causes localised vasoconstriction and platelet aggregation → haemostasis
- NSAIDs inhibit platelet COX-1 → ↓ TXA₂ → impaired haemostasis 2° to ↓ platelet aggregation and ↓ vasoconstriction

Note – Anti-platelet effects of Aspirin last for the lifespan of a platelet (10-14 days) → b/c (i) platelets cannot regenerate new COX (as they lack nuclei) and (ii) COX inhibition is irreversible → thus, need to wait for new platelets and COX-1 to regenerate

- COX-2 selective inhibitors have NO effect on platelets (even at high doses) as platelets do NOT contain COX-2 → instead, they are PRO-THROMBOTIC (see below)

(5) Hepatotoxicity:

- Transient transaminitis (reversible liver damage) occurs with short term use
- Rare severe hepatic dysfunction (jaundice and liver failure) occurs with prolonged or excessive use (see “Paracetamol toxicity” above)

(6) Cardiovascular effects:

- (i) Systemic HTN – PGs normally counter the effects of vasoconstrictor hormones on arteriolar SM, and have a natriuretic effect → NSAIDs inhibit these PG functions, thus causing net arteriolar vasoconstriction and $\text{Na}^+/\text{H}_2\text{O}$ retention
- (ii) Arterial thrombosis (Eg. ↑ MI/CVA) → esp with prolonged COX-2 selective inhibitor therapy (esp rofecoxib)

Mechanism – COX-2 selective inhibitors alter the PGI₂-TXA₂ ratio in favour of a pro-thrombotic environment → this is because they:

- (i) Selectively inhibit vascular endothelium synthesis of PGI₂ → lose vasodilatory effect and inhibitory effect on platelet aggregation
- (ii) Do not inhibit platelet synthesis of TXA₂ (as platelets possess only COX-1) → TXA₂ is continuously produced causing platelet aggregation and vasoconstriction

- (iii) Heart failure → mainly a/w COX-2 selective inhibitors

(7) Drug interactions:

- (i) NSAID + anticoagulant (Eg. heparin, warfarin) → potentiates bleeding (esp GI bleeding)

Important to note – NSAIDs displace warfarin from plasma protein → ↑ free fraction of warfarin → need to monitor INR closely

- (ii) Aspirin + NSAIDs (including COX-2 selective inhibitors) → ↑ risk of GI toxicity
- (iii) NSAIDs + K^+ -sparing diuretics → hyperkalaemia
- (iv) NSAID + lithium, digoxin or aminoglycosides → NSAID-induced renal dysfunction reduces the clearance of these drugs, thus close drug level monitoring is required
- (v) NSAID + β -blockers, diuretics, ACEi → interfere with anti-hypertensive effects 2° to ↑ $\text{Na}^+/\text{H}_2\text{O}$ retention

(8) Others:

- (i) Allergy are rare → main issue is sulphonamide sensitivity a/w celecoxib and valdecoxib
- (ii) Impaired bone healing
- (iii) Aseptic meningitis → more commonly occurs with ibuprofen and women with underlying autoimmune diseases (a/w acute hypersensitivity reaction)
- (iv) Obstetrics issue – Prolongs labour and ↑ PPH risk (due to loss of uterotonic effects and platelet dysfunction), and risk of premature ductus arteriosus closure

- (h) *To describe the pharmacology of the injectable NSAIDs (ketorolac, diclofenac and parecoxib).*

See sections on “ketorolac”, “diclofenac”, and “parecoxib” above.