

ACETAZOLAMIDE / DIURETIC

Acetazolamide, whilst considered a class of diuretics is **rarely used for this purpose** because excess carbonic anhydrase it requires very high doses to be effective and **due to the loss of HCO_3^-** associated with its use causes a metabolic acidosis and urinary alkalinisation. It is mainly used for the treatment of **glaucoma** and **altitude sickness** and may be used as an adjunct in **epilepsy** (increased CO_2 decreases seizure spread).

PHARMACEUTICAL ASPECTS

It is presented as a white tablet with a dose of 250mg.

PHARMACODYNAMIC ASPECTS

Inhibits carbonic anhydrase in the **proximal tubule** cells which therefore **reduces the production of H^+ and HCO_3^- from H_2O and CO_2** which CA normally catalyses. This theoretically leads to a decrease in sodium excretion via the sodium-H antiporter, and thus increased water excretion. In the **eye** it blocks the same reaction but the decreased is the most important aspect leading to **less aqueous humour secretion** and therefore lowers intraocular pressures.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability ~100%
routes of administration oral (IV also possible)
doses glaucoma 250mg q6hr
onset / duration

DISTRIBUTION

lipid solubility **crosses BBB**
protein binding highly protein bound

METABOLISM

mechanism **not metabolised**

ELIMINATION

half life 6–9 hours
excretion Urine (**70% to 100% as unchanged drug**)

MAJOR ISSUES OR SIDE EFFECTS

Up to 50% of patients prescribed acetazolamide do not tolerate its side effects.

Most side effects related to the **metabolic acidosis** and **urinary alkalinisation**.

Contraindicated in patients with acidosis, may worsen sodium and potassium depletion. Can cause paresthesias, fatigue, drowsiness, depression, n+v, abdominal pain.

ADENOSINE / OTHER ANTIARRHYTHMIC

Adenosine is a natural purine nucleoside. It slows conduction through the atrioventricular node which makes it an effective treatment for the termination of paroxysmal SVT. It is also used sometimes for slowing rapid atrial arrhythmias to aid diagnosis.

PHARMACEUTICAL ASPECTS

Adenosine is only available as a clear liquid with 6mg in 2mL.

PHARMACODYNAMIC ASPECTS

It acts on the A1 adenosine receptors found in the SA and AV. It markedly slows or completely blocks conduction in the atrioventricular node, probably by hyperpolarizing this tissue (through increased I_{K1}) and by reducing calcium current. This causes a temporary heart block and/or asystolic pause which acts to terminate the supra ventricular rhythm.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV only
doses 3-6mg as a bolus
onset / duration seconds / seconds

DISTRIBUTION

volume of distribution not applicable

METABOLISM

mechanism Rapidly deaminated in plasma and taken up by red blood cells

ELIMINATION

half life <10 seconds

MAJOR ISSUES OR SIDE EFFECTS

Because of its short half life the side effects are transient but can be distressing for patients (sense of impending doom). It may induce AF or flutter due to the reduced refractory period. It is contraindicated in sick sinus syndrome. It is avoided in asthmatics and pts with COPD as it may cause bronchospasm.

ADRENALINE/ CATECHOLAMINE

Is a **naturally occurring catecholamine** that is released the **adrenal medulla**. It is used in a critical care setting for **maintenance of haemodynamic parameters** via increase in total peripheral resistance, in arrest situations as part of the **ACLS protocols** and in the setting of **bronchoconstriction** and **anaphylaxis** as a mast cell stabiliser. It is an additive in **local anesthetics** to lower dosage by causing local vasoconstriction.

PHARMACEUTICAL ASPECTS

It is presented in clear solution only, usually 1mg/mL in 5 and 50 mL vials and in **minijets** with **1mg in 10mL (1:10000)**. It also comes in combination with lignocaine for local anaesthesia with a concentration of 1:80000-200000. It may also be nebulised. It is **not stable in an alkaline solution** as it oxidises to adrenochrome and turns pink, therefore it is usually in an acidic solution.

PHARMACODYNAMIC ASPECTS

It is a **non selective adrenergic agonist**. At **lower doses** it has **vasodilatory effects** and **bronchial dilation via beta2 receptors**. At **higher doses** beta1 agonism leads to **increased inotropy and chronotropy**. At the **highest doses** it is primarily a **vasoconstrictor**. It also **stabilises mast cells** which is why it is used in acute anaphylaxis.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration **IV, IM, SC, Inhaled, ETT**
doses 1mg in arrest, 0.1mg in anaplexis,
infusion dose is 0.1-0.3mcg/kg/min beta effects
>0.3mcg/kg/min for alpha (vasoconstrictive effects)
onset / duration immediate / 1-2 minutes

DISTRIBUTION

lipid solubility **doesn't cross the BBB**

METABOLISM

mechanism Taken up into the adrenergic neuron and metabolized by monoamine oxidase and catechol-o-methyltransferase; circulating drug hepatically metabolized

ELIMINATION

half life **2 minutes**
excretion Urine as inactive metabolites,

MAJOR ISSUES OR SIDE EFFECTS

High doses cause **severe hypertension, tachyarrhythmias**, and **deranged metabolic states** with increased glucogenolysis, lipolysis and gluconogenesis. Insulin production is initially increased (beta2) but later decreased (alpha) **limiting use in DM**. **Can worsen PHTN**. **Avoid in glaucoma**. **Peripheral necrosis** may occur.

ALFENTANIL / SYNTHETIC OPIOID

Is a synthetic phenylpiperidine. It is a μ receptor agonist and therefore has a mode of action similar to morphine. Pharmacokinetic features, in particular the pKa ensure however significant differences to the related opioids such as fentanyl. It is marketed as an induction agent but is usually used for its analgesic properties.

COMPARED TO FENTANYL

Both synthetic phenylpiperidine derivatives, Alfentanil 1/5th as potent, Effect-site equilibration time = 1.4 min, pKa = 6.5, 10x as much alfentanil present in unionised form at pH 7.4, More rapid transfer across blood brain barrier, Only 10% 1st pass pulmonary uptake for alfentanil, Alfentanil lower clearance rate but shorter t_{1/2} 10x variability in alfentanil clearance because of interpersonal variability of CYP3A4 Lower Vd (4-6x smaller than fentanyl), Less lipid soluble, Both 85-90% protein bound Alpha 1 acid glycoprotein, Alfentanil has sorter context sensitive half time following prolonged infusions

PHARMACEUTICAL ASPECTS

Alfentanil is presented as a colourless solution containing 500mcg/ml in 2 of 5ml vials.

PHARMACODYNAMIC ASPECTS

It has the same mode of action and generally similar effects to morphine

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV
doses 7mcg/kg up to 50 mcg/kg if ventilated
onset / duration rapid / 30-60 minutes

DISTRIBUTION

volume of distribution 0.5 L/kg (much lower than fentanyl)
protien binding 85-90%
lipid solubility less than fentanyl (more than morphine)
pKa 6.5, mostly non ionised therefore crosses the BBB rapidly

METABOLISM

mechanism Liver by N - demethylation

ELIMINATION

half life 1.5 hours (shorter context sensitive compared fent
excretion urine

MAJOR ISSUES OR SIDE EFFECTS

as per other opiates

GENTAMICIN / AMINOGLYCOSIDE

Gentamicin is the aminoglycoside of choice because of its lower cost and reliable activity against gram negative bacillary infections. It is often used in combination with a beta lactam antibiotic for serious but uncultured infections. They also have limited gram positive coverage including staph and some strep.

PHARMACEUTICAL ASPECTS

Presented as clear solution for injection. Requires monitoring of levels especially if there is any renal impairment, to prevent complications.

PHARMACODYNAMIC ASPECTS

Aminoglycosides are bactericidal antimicrobials that block protein synthesis by binding to the bacterial 30S ribosomal subunit.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability no oral absorption, rapid and complete IM routes of administration IV (poor lipid solubility) doses 3-10mcg/kg depending on severity onset / duration 30mins
DISTRIBUTION	volume of distribution 0.2-0.3 L/kg protein binding <30% lipid solubility low lipid solubility - reduces gut absorption some CSF penetration with inflamed meninges (30%)
METABOLISM	mechanism not metabolised
ELIMINATION	half life 1.5-3 hrs, +++ in renal impairment (up to 70hrs) excretion urine as unchanged drug

MAJOR ISSUES OR SIDE EFFECTS

Dose dependent nephrotoxicity and ototoxicity. May cause C.Diff overgrowth. They decrease the presynaptic release of acetylcholine, which reduces post junctional sensitivity to acetylcholine and therefore increases NDMR activity and cause muscle weakness.

AMIODARONE / CLASS III (ALL CLASS ACTIONS)

Amiodarone is a **benzofuran derivative** which contains **37% iodine** by weight and structurally **resembles thyroxine**. Although usually considered a class III antiarrhythmic it displays **actions of all four classes**. It is now preferred over procainamide and lignocaine for the treatment of **unstable VT and VF**. It is also used for SVT, VT and WPW and **off label for most arrhythmias in a critical care setting**.

PHARMACEUTICAL ASPECTS

It is presented in 100mg and 200mg tablets and as a clear fluid with a concentration of 50mg/mL. It has a therapeutic concentration range of 1-2.5mg/L but monitoring is rarely necessary.

PHARMACODYNAMIC ASPECTS

As noted it has all class actions, It blocks sodium, calcium, and potassium channels and adrenoceptors. The result is a prolonging of the effective refractory period of all cardiac tissues, including the sinoatrial node, atrium, atrioventricular node, His-Purkinje system, and ventricle.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** **poorly absorbed, bioavailability 40-70%**
routes of administration PO/IV
doses PO 200mg TDS 1/52, BD 1/52, then OD, 5mg/kg over one hour then 15mg/kg over 24 hours IV
onset / duration **2 days to 3 weeks / 1 week to 5 months**

DISTRIBUTION **volume of distribution** **66 L/kg (range: 18-148 L/kg)**
protein binding **96%**

METABOLISM **mechanism** **Hepatic via CYP2C8 and 3A4 to active N-desethylamiodarone metabolite**

ELIMINATION **half life** **Terminal: 40-55 days**
excretion **Faeces, urine, skin and lachrymal glands**

MAJOR ISSUES OR SIDE EFFECTS

Amiodarone has **major side effects** that worsen over time and affect most patients. Respiratory - it may cause **pneumonitis, fibrosis or pleuritis**. Endocrine - it may cause **hypothyroidism (6%) or hyperthyroidism (1%)**. Hepatic - it is associated with cirrhosis, hepatitis and jaundice. **LFT monitoring** is recommended. Ophthalmic - **corneal microdeposits** occur commonly but usually resolve on cessation. Cardiac - it is **not particularly arrhythmogenic despite QT prolongation** (likely because of its multiple actions) but **can cause bradycardia and hypotension**.

Christopher Andersen 2012

AMPICILLIN / BETALACTAM ANTIBIOTIC

Ampicillin is an aminopenicillin and is also known as a broad spectrum penicillin. It is effective against the same range of organisms as benpen but because it is more hydrophilic it penetrates the pores of the outer phospholipid membrane of gram negatives thus giving it some activity against some H. influenza, Salmonella, E. coli and E. faecalis. It is inactivated by beta-lactamases and may be given with clavulanic acid.

PHARMACEUTICAL ASPECTS

May be given orally or parenterally, however amoxycillin is preferred orally due to its improved oral bioavailability. It is marketed under several trade names in Australia.

PHARMACODYNAMIC ASPECTS

Beta-lactam antibiotics inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, which are involved in the third stage of cell wall synthesis. It is during this stage that linear strands of peptidoglycan are cross-linked, beta lactams prevent this linking occurring.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 50%
routes of administration PO, IV or IM
doses Usually given QID or TDS in up to 70mg/kg/day

DISTRIBUTION

volume of distribution ~0.38 L/kg
protein binding 15% to 25%
lipid solubility penetration into CSF occurs with inflamed meninges only

METABOLISM

mechanism Minimal metabolism

ELIMINATION

half life 1-1.8 hours, prolonged in anuria/renal impairment
excretion Urine (90% as unchanged drug) within 24 hours

MAJOR ISSUES OR SIDE EFFECTS

Up to 10% of the population have allergies to penicillins. Due to the high percentage excreted renally unchanged dose adjustment is required in low urine output states.

ASPIRIN / IRREVERSIBLE NONSELECTIVE NSAID

Aspirin (**acetylsalicylic acid**) is a non selective non steroidal antiinflammatory drug which is used for its analgesic, anti inflammatory and its irreversible binding to platelets and subsequent reduction of thromboembolic events such as acute myocardial infarction and stroke.

PHARMACEUTICAL ASPECTS

Aspirin is usually presented as 300mg or 100mg tablets.

PHARMACODYNAMIC ASPECTS

Irreversibly inhibits cyclooxygenase-1 and 2 (**COX-1 and 2**) enzymes, via acetylation, which results in **decreased formation of prostaglandin precursors**; irreversibly inhibits formation of prostaglandin derivative, thromboxane A₂, via **acetylation of platelet cyclooxygenase**, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** Rapid, **50%-75%** reaches systemic circulation
routes of administration oral
doses 100mg for antiplatelet, 300-900mg other
onset / duration 4-6 hours

DISTRIBUTION **volume of distribution** **Vd: 10 L**;
protein binding 85% mostly albumin
pKa **3 weak acid**, mostly non ionised, therefore good gastric absorption, although may become trapped in mucosal cells.
most absorption is therefore in the small bowel)

METABOLISM **mechanism** **Hydrolyzed to salicylate (active) by esterases** in GI mucosa, red blood cells, synovial fluid, metabolism of salicylate occurs primarily by hepatic conjugation; **metabolic pathways are saturable**

ELIMINATION **half life** **Parent drug: 15-20 minutes; Salicylates (dose dependent): 3 hours at lower doses (300-600 mg), 5-6 hours (after 1 g), 10 hours with higher doses**
excretion Urine (75% as salicyluric acid, 10% as salicylic acid)

MAJOR ISSUES OR SIDE EFFECTS

Normal NSAID side effects. See AI summary regarding toxicity.
Christopher Andersen 2012

ATROPINE / ANTICHOLINERGIC

Atropine is a naturally occurring **tertiary amine** derived from the belladonna plant. Its anticholinergic activity is used to **antagonize** the muscarinic effects produced by **anticholinesterase drugs**, in the management of intraoperative **bradycardia** during general anaesthesia, or in the treatment and diagnosis of **organophosphate poisoning**. In ophthalmology it is used to induce **mydriasis and cycloplegia** to aid examination.

PHARMACEUTICAL ASPECTS

Atropine's anticholinergic activity is primarily due to the **L enantiomer** although it is presented as a **racemic mixture**. Although previously available in oral formulations it is only available for topical application to the eye.

PHARMACODYNAMIC ASPECTS

Low doses of atropine (2mcg/kg) act centrally and may **augment vagal outflow**, decreasing heart rate. At **normal clinical doses** (15-70mcg/kg) atropine also acts on peripheral muscarinic receptors **blocking** the action of the **vagal nerve** and **increasing the heart rate** and **pupil size** whilst **decreasing secretory gland activity**. The latter is particularly important in cholinergic poisoning to reduce bronchorrhoea and bronchoconstriction. Other effects include reduced tone in the gut, bile ducts, and contractions in the ureter and bladder.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100% (Oral)
routes of administration IV
doses 15-70 mcg/kg
onset / duration rapid / 1-2 hours

DISTRIBUTION

volume of distribution 1-2 l/kg **rapidly distributed from central compartment** on administration
protein binding 50% plasma bound

METABOLISM

mechanism extensively metabolised by **liver esterases**

ELIMINATION

half life 2-3 hours
excretion **urine (fraction unchanged)**

MAJOR ISSUES OR SIDE EFFECTS

Although less pronounced than scopolamine (hyoscine) high doses and overdose of atropine may cause a **central anticholinergic syndrome** characterised by excitement, hallucinations and hyperpyrexia. In overdose this leads to coma, respiratory depression and death.

Christopher Andersen 2012

BENZYL PENICILLIN / BETA LACTAM ANTIBIOTIC

Benzyl penicillin was the first penicillin and remains an important antibiotic today. It is also known as penicillin G. Its spectrum of coverage includes gram positive pathogens, gram negative cocci and some gram negative bacilli. Its most common use is for treating streptococci, syphilis and nisseria.

PHARMACEUTICAL ASPECTS

It is inactivated by the acid in the stomach so is therefore normally delivered parenterally either IM or IV. In Australia its trade name is BenPen. It is presented as a powder for reconstitution.

PHARMACODYNAMIC ASPECTS

Beta-lactam antibiotics inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, which are involved in the third stage of cell wall synthesis. It is during this stage that linear strands of peptidoglycan are cross-linked, beta lactams prevent this linking occurring.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	Poorly available orally due to low gut pH.
	routes of administration	IV or IM
	doses	Usually given QID in up to 24g/day
DISTRIBUTION	volume of distribution	~0.35 L/kg
	protein binding	65%
	lipid solubility	Poor penetration across blood-brain barrier, slight improvement with inflamed meninges
METABOLISM	mechanism	Hepatic (30%) to penicilloic acid
ELIMINATION	half life	Normal renal function: 30-50 minutes
	excretion	Urine (58% to 85% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Up to 10% of the population have allergies to penicillins. Due to the high percentage excreted renally unchanged dose adjustment is required in low urine output states. High doses used in critical care settings lower seizure thresholds. Benpen has a high sodium content.

Christopher Andersen 2012

BUPIVACAINE / LOCAL ANAESTHETIC

(including LEVOBUPIVACAINE and ROPIVACAINE)

Is an **amide local anaesthetic**. It is used primarily in **spinal and epidural anaesthesia**. It may be prepared in a concentrated glucose solution (80mg/mL), this is marketed as 'heavy' marcain.

PHARMACEUTICAL ASPECTS

It is presented as a **racemic mixture**. An alternative presentation is levobupivacaine which is as the name suggests only the S (-) enantiomer which is less cardiotoxic. Ropivacaine is a very similar drug it is also only the S (-) enantiomer with marginally different amide side chain, this confers reduced toxicity and slightly decreased potency (lipid solubility)

PHARMACODYNAMIC ASPECTS

Similar to lignocaine they block nerve conduction by **inhibiting voltage gated sodium channels at an intracellular site** probably within the pore of the channel. Local anaesthetics once bound to the channel **stabilise and prolong the duration of the inactivated state**, thus preventing sodium channel opening during further depolarisations. **Sensory function is more sensitive** to local anaesthetic block than motor function possibly due to greater sensitivity of the **small myelinated fibres**.

PHARMACOKINETIC ASPECTS

ABSORPTION	routes of administration	SC, IM, Intrathecal
	dose	15-20mg intrathecally
	Max dose	2mg/kg with or without adrenaline
	onset / duration	route and dose dependent 1-15min/ 2-9 hrs
DISTRIBUTION	protein binding (duration)	~95% higher than lignocaine
	lipid solubility (potency)	higher than lignocaine
	pKa (onset)	8.1 higher than lignocaine = slower onset
METABOLISM	mechanism	Hepatic;
ELIMINATION	half life	2.7 hours
	excretion	Urine (~6% unchanged)

MAJOR ISSUES OR SIDE EFFECTS

Has the **same issues as lignocaine but at lower doses**. The **R enantiomer** seems to **cause cardiac issues** earlier than the S enantiomer **hence** the development of **levobupivacaine** and the S enantiomer **ropivacaine**.

CAPTOPRIL / ACE INHIBITOR

Captopril is an active drug converted to active metabolites. It is a competitive ACE inhibitor that is used for management of hypertension, LV dysfunction post myocardial infarction and in the setting of heart failure. Its use has been shown to decrease progression of heart failure (disease modifying).

PHARMACEUTICAL ASPECTS

It is an oral formulation presented as white tablets in dosage ranging from 12.5mg to 50mg.

PHARMACODYNAMIC ASPECTS

Cardiovascular - Competitive inhibition of angiotensin converting enzyme leads to decreased angiotensin II production and its effects. TPR and Afterload is decreased to a greater extent than preload, and this may result in improved CO in heart failure patients. HR is usually unchanged and baroreceptor reflexes also unchanged. **Renal**- the impairment of AngII means that the body is less able to respond to a drop in renal perfusion and this may precipitate failure. **Metabolic** - Accumulation of K^+ may occur due to decreased aldosterone.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability rapidly absorbed, bioavailability of 60-70% routes of administration oral doses commenced at 6.25mg TDS and uptitrated potency moderately potent
DISTRIBUTION	protein binding 25% protein bound
METABOLISM	mechanism oxidised in the liver and converted to sulphides
ELIMINATION	half life 2-4 hours excretion urine both as active metabolites and unchanged

MAJOR ISSUES OR SIDE EFFECTS

A dry cough may occur especially in patients with pre-existing lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

CARVEDILOL / BETA & ALPHA BLOCKER

Carvedilol is a third generation non selective beta blocker with alpha 1 antagonist properties. It is used to reduce the excessive adrenergic activity that occurs in response to heart failure. It may be also used in the treatment of hypertension.

PHARMACEUTICAL ASPECTS

It is only available in oral form in both immediate and sustained release formulations.

PHARMACODYNAMIC ASPECTS

Beta blockage leads to decreased G_s activity in receptor associated organs and associated decrease in adenylyl cyclase and intracellular Ca^{2+} . It produces decreases in heart rate and cardiac output and myocardial oxygen consumption. Alpha blockage leads to decrease G_q activation and subsequent decrease in IP_3 and intracellular Ca^{2+} .

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** rapid and extensive absorption but high first pass metabolism leading to bioavailability of 25-35%
routes of administration oral
doses start at 6.25 BD and doubled 1/52 until not tolerated

DISTRIBUTION **volume of distribution** 105 L/kg
protein binding 98% to albumin
lipid solubility moderate lipid solubility

METABOLISM **method** Extensively hepatic, via CYP2C9, 2D6, 3A4, three active metabolites

ELIMINATION **half life** 7-8 hours
excretion in faeces

MAJOR ISSUES OR SIDE EFFECTS

Similar to other betablockers with respect to the withdrawal aspects, use in the setting of COPD and with Ca Channel blockers and Halothane. Due to its metabolism it should be used in caution in liver failure patients and elderly.

Christopher Andersen 2012

CEFTRIAXONE / CEPHALOSPORIN

"Ceftriaxone" is a third-generation cephalosporin antibacterial used for the treatment of infections caused by susceptible Gram-positive and Gram-negative bacteria, including infections of the abdomen, bones and joints, CNS, skin and skin structures, genito-urinary tract (including gonorrhoea), respiratory tract, gynaecological infections, and early Lyme disease.

PHARMACEUTICAL ASPECTS

Clear solution for injection

PHARMACODYNAMIC ASPECTS

Inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs) which in turn inhibits the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis. Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	Well absorbed when given IM
	routes of administration	IV/IM
	doses	1-2 g daily
	onset / duration	serum peak in 2-3 hrs (following IM inj)
DISTRIBUTION	volume of distribution	6-14L
	protein binding	85-95%, may lead to non linear dose dependent responses
	lipid solubility	crosses the BBB regardless of meningeal infl
METABOLISM	mechanism	only partial
ELIMINATION	half life	up to 8 hours enabling daily dosing
	excretion	urine 33-66% unchanged and in the bile

MAJOR ISSUES OR SIDE EFFECTS

highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates. Biliary sludge or pseudolithiasis due to a precipitate of calcium "ceftriaxone" has been seen occasionally in patients given "ceftriaxone".

CIPROFLOXACIN / FLUOROQUINOLONE

Ciprofloxacin is a fluoroquinolone which inhibits nucleic acid synthesis. It is active against a wide range of gram negative and some gram positive bacteria (streptococcus and enterococcus have moderate sensitivity).

PHARMACEUTICAL ASPECTS

Is available in both oral and IV formulations (clear solution). Marketed under several trade names including ciproxin.

PHARMACODYNAMIC ASPECTS

The quinolones are bactericidal antimicrobials that inhibit the alpha subunit of the DNA gyrase enzyme. This enzyme is responsible for the negative supercoiling of bacterial and when activated rapidly results in cell death.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Oral: Rapid (~50% to 85%)
routes of administration IV and PO
doses 250-750mg PO BD or 200-300mg IV BD
onset / duration peak concentration in 2hrs PO

DISTRIBUTION

volume of distribution 2.1-2.7 L/kg, tissue concentrations may exceed serum concentrations
protein binding 20% to 40%
lipid solubility 10% CSF penetration (up to 40% with inflamed meninges)

METABOLISM

mechanism Partially hepatic; metabolites (limited activity)

ELIMINATION

half life 3-5 hrs, extended in renal failure
excretion Urine (30% to 50% as unchanged drug); feces (15% to 43%)

MAJOR ISSUES OR SIDE EFFECTS

Can cause issues with G6PD patients, may cause nausea, vomiting and abdominal pain. Caution in epileptic patients as it may cause seizures, confusion and restlessness. Some issues with anaphylaxis.

Christopher Andersen 2012

CLONIDINE / CENTRAL ALPHA₂ AGONIST

Clonidine is a partial alpha agonist with an affinity for alpha₂ receptors 200 times that for alpha₁ receptors. In addition to its use in refractory hypertension it is also used as an adjunct in pain management and during anaesthesia. It has been used in patients withdrawing from opioids and for the diagnosis of pheochromocytoma.

PHARMACEUTICAL ASPECTS

It is available both in oral form as a white tablet in dosages of 100-150mcg and IV/IM forms as a colourless solution with 150mcg/ml.

PHARMACODYNAMIC ASPECTS

The useful effects of clonidine rest on its ability to stimulate alpha₂ receptors in the lateral reticular nucleus resulting in decreased central sympathetic outflow by a positive feedback mechanism, and in the spinal cord where it augments endogenous opiate release and modulates descending noradrenergic pathways. Cardio - transient increase in BP due to alpha₂ agonism peripherally but this is followed by a more prolonged fall in BP. CO is usually maintained despite bradycardia. CNS - sedation and anxiolysis at low doses but anxiogenic at higher doses. Provides analgesia without respiratory centre depression and is synergistic with opioids. Renal - inhibition of ADH may be the cause of diuresis. Endocrine-stress response to surgery inhibited. Insulin release is reduced, usually BSL ok.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Immediate release: 75% to 85%
routes of administration Oral, IV and IM
doses usually 150-300mcg twice daily

DISTRIBUTION

volume of distribution 2.1 L/kg
protein binding 20% to 40%
lipid solubility highly lipid soluble in order to cross the BBB

METABOLISM

mechanism Extensively hepatic to inactive metabolites

ELIMINATION

half life 12-16 hours (increased in pts with renal disease)
excretion Urine (40% to 60% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

The multiple effects of this drug make it intolerable to many patients, with somnolence and dry mouth being a frequent concern. It may cause profound bradycardia if used with beta blockers. If withdrawn suddenly it may cause a rebound hypertension.

Christopher Andersen 2012

CLOPIDOGREL / PLATELET ADP ANTAGONIST

Clopidogrel is a thienopyridine derivative which acts as a non competitive antagonist of platelet surface ADP, which is responsible for platelet aggregation. It is used for prevention of vascular ischaemic events, as an adjuvant in the treatment of NSTEMI (when grafting is not indicated) and in the management of patients post stenting.

PHARMACEUTICAL ASPECTS

It is presented as 75mg tablets. A loading dose of 300mg should be used when instigating treatment. It's trade name is Plavix.

PHARMACODYNAMIC ASPECTS

Clopidogrel irreversibly prevent ADP from binding to its receptor on the platelet surface, thereby preventing the glycoprotein IIb/IIIa receptor transforming into its active form.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Well absorbed
routes of administration oral
doses 300mg loading, 75mg daily
onset / duration 2hrs / 5 days

DISTRIBUTION

volume of distribution
protein binding Parent drug: 98%; Inactive metabolite: 94%

METABOLISM

mechanism Extensively hepatic via esterase-mediated hydrolysis, active metabolite and inactive metabolite

ELIMINATION

half life Parent drug: ~6 hours; Active metabolite: ~30 mins
excretion Urine (50%); feces (46%)

MAJOR ISSUES OR SIDE EFFECTS

Commonly causes GI irritation. Issues with haemorrhage. Rarely causes neutropenia.

DEXMEDETOMIDINE / CENTRAL α_2 AGONIST

Is a central α_2 agonist which is primarily used for its sedating properties for the short term management of intubated patients. It has greater selectivity and potency than clonidine with an $\alpha_1:\alpha_2$ ratio of 1:1600.

PHARMACEUTICAL ASPECTS

Medetomidine is a racemic mixture but only the D-Stereoisomer is active, so it has been developed as dexmedetomidine. Although textbooks indicate that oral preparations exist in Australia its usage is IV only.

PHARMACODYNAMIC ASPECTS

Broadly similar to clonidine although sedative and analgesic aspects predominate. It is believed that this is due to central activation of α_2 adrenoceptors in the locus coeruleus. Peripheral α_2b -adrenoceptors are activated at high doses or with rapid I.V. administration resulting in vasoconstriction. Its lack of respiratory depression increases its utility in the ICU setting.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability IV therefore 100%

routes of administration IV

doses Usually 1mcg/kg over 20 minutes, then a maintenance dose of 0.2-0.7 mcg/kg per hour titrated

onset of action I.V. Bolus: 5-10 minutes

DISTRIBUTION

volume of distribution V_{ss} : ~118 L

protein binding ~94%

lipid solubility

METABOLISM

mechanism Hepatic via N-glucuronidation, N-methylation, and CYP2A6

ELIMINATION

half life ~6 minutes;

excretion Urine (95%); feces (4%)

MAJOR ISSUES OR SIDE EFFECTS

There may be a transient hypertension on commencement followed by hypotension and bradycardia. Other side effects include dry mouth, hypotension, bradycardia and the risk of a rebound hypertension on withdrawal.

DIAZEPAM / BENZODIAZEPINE

Is a benzodiazepine used for the management of anxiety disorders, ethanol withdrawal symptoms; skeletal muscle relaxant; treatment of convulsive disorders; preoperative or preprocedural sedation and amnesia.

PHARMACEUTICAL ASPECTS

Available in a range of different formulations, tablets, oral suspension, rectal gel, IV. Trade name valium.

PHARMACODYNAMIC ASPECTS

Benzodiazepines appear to produce all their pharmacologic effects by facilitating the actions of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. Benzodiazepines do not activate GABA_A receptors but rather enhance the affinity of the receptors for GABA. As a result of this drug-induced increased affinity of GABA receptors for the inhibitory neurotransmitter, an enhanced opening of chloride gating channels results in increased chloride conductance, thus producing hyperpolarization of the postsynaptic cell membrane

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Oral: 85% to 100%
routes of administration PO, IV, IM
doses 5-20mg PO
onset / duration IV rapid onset / prolonged action

DISTRIBUTION

volume of distribution 1-1.5 L/kg (same as midazolam)
protein binding 98%
lipid solubility v. high

METABOLISM

mechanism Hepatic oxidation, slow clearance and +++
context sensitive half time if delivered as infusion. Reduce dose in liver failure. clearance is much slower than midaz

ELIMINATION

half life Parent drug: 20-50 hours Active major metabolite (desmethyldiazepam): 50-100 hours
excretion

MAJOR ISSUES OR SIDE EFFECTS

Main issues are from overdosage and excessive sedation and depression of respiratory drive. Causes tolerance and dependence and may precipitate withdrawals if ceased following long term use.

DIGOXIN / OTHER ANTIARRHYTHMIC, INOTROPE

Digoxin is a **glycoside derived from the dried leaves of the foxglove**. It is used in AF and atrial flutter, SVT and in heart failure

PHARMACEUTICAL ASPECTS

Digoxin is available in oral tablets 62.5mcg or 250mcg and injectable for with a concentration of 25-250mcg/ml. There is a **narrow therapeutic window and monitoring is necessary**, with most aiming for the lower range of 0.5-2mcg/L concentrations (often around 1mcg/L)

PHARMACODYNAMIC ASPECTS

The direct effect of digoxin is via **Inhibition of Na^+/K^+ ATPase** is considered to be the primary biochemical mechanism of action. Then higher intracellular Na **reduces action of the Na-Ca pump** leading to decreased calcium extrusion and therefore **increased intracellular Ca** therefore **increased inotropy**. Other direct effects include an increased AV node refractory node period but decreased ventricle refractory period. Indirect effects are mediated by the vagus nerve and include bradycardia, reduced refractory period in the atrial muscle and an augmentation of the direct **increase in AV node refractory period**. It is the AV node actions **and bradycardia which are effective treating AF and Flutter**.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 60% to 80%
routes of administration PO / IV
doses loading 250-500mcg QID then 62.5-125mcg daily
onset / duration Oral: 1-2 hours; I.V.: 5-60 mins / **3-4 days**

DISTRIBUTION

volume of distribution 6-7 L/kg **thyroid status important**
protein binding ~25%; in uremic patients, digoxin is displaced from plasma protein binding sites

METABOLISM

mechanism Via sequential sugar hydrolysis in the stomach or by reduction of lactone ring by intestinal bacteria ,
minimal hepatic metabolism, most excreted unchanged

ELIMINATION

half life 36-48 hours
excretion Urine (50% to 70% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Thyroid function has significant effects on V_0 increasing in hyper and decreasing in hypothyroidism. It is **toxic above concentrations of 2.5mcg/L** causing **arrhythmias**, and **AV block**. It also causes anorexia, nausea and vomiting, diarrhoea and lethargy. **Red green colour perception** may be altered. **ECG changes** include **prolonged PR, ST depression, T wave flattening and QT shortening** (may not indicate toxicity).

Christopher Andersen 2012

DILTIAZEM / Ca²⁺ CHANNEL BLOCKER

Diltiazem is a nondihydropyridine calcium channel blocker. It is used for angina and hypertension.

PHARMACEUTICAL ASPECTS

Is available in sustained and immediate release oral formulations, 60-360mg

PHARMACODYNAMIC ASPECTS

Similar to the other Ca Channel blockers in terms of blood pressure. Produces more peripheral vasodilation than verapamil and more conduction delay than the dihydropyridines such as nifedipine.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability Well absorbed high first pass metabolism leading to bioavailability of 40%
	routes of administration oral or IV
	doses 30-80mg TDS
	onset / duration tablet: 30-60 minutes; I.V.: 3 minutes
DISTRIBUTION	volume of distribution 3-13 L/kg
	protein binding 70% to 80%
METABOLISM	mechanism Hepatic active metabolites desacetyldiltiazem
ELIMINATION	half life 3-4.5 hours (prolonged in renal failure)
	excretion Urine (4% as unchanged, 7% as metabolites); feces

MAJOR ISSUES OR SIDE EFFECTS

Peripheral oedema is a common side effect, 2-3 weeks post initiation of therapy. Other side effects include flushing, vertigo, headaches, hypotension and parathesias.

DIPYRIDAMOLE / PLATELET PDE INHIBITOR

Dipyridamole acts by **inhibiting phosphodiesterase**, which increases platelet cAMP and inhibits platelet aggregation. It's main use is in the **prevention of stroke** when in combination with aspirin. It may have a marginal additive benefit in patients with **prosthetic heart valves** when used in combination with warfarin. It is a potent vasodilator and is sometime used in **cardiac function testing**.

PHARMACEUTICAL ASPECTS

It is available in **both oral and IV** formulations and is known as **persantin**. In combination with aspirin it is traded as **asasantin**. If take orally it should be taken **away from meals** as this leads to variable absorption.

PHARMACODYNAMIC ASPECTS

Dipyridamole **inhibits platelet adhesion** to damaged vessel walls (by inhibiting adenosine uptake), **potentiates** the affects of **prostacyclin** and at high doses inhibits platelet phosphodiesterase activity resulting in **increased cAMP levels** and **lower intraplatelet calcium levels**. Compared to aspirin it inhibits platelet adhesion to vessel walls more than aggregation. It is a **potent coronary artery dilator** via the phosphodiesterase inhibition mechanism.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability variable depending on concurrent oral intake
	routes of administration IV and oral
	doses 200mg BD for CVA prevention
	onset / duration onset is within 1 hr, peak 2hrs

DISTRIBUTION	volume of distribution 2-3 L/kg
	protien binding 90-99%

METABOLISM	mechanism hepatic glucoridation, incomplete
------------	---

ELIMINATION	half life 10-12 hours
	excretion faeces as glucuronides and unchanged

MAJOR ISSUES OR SIDE EFFECTS

Major **side effects** relate to its **vasodilatory properties** making it **unsafe** in patients with **recent MIs** and **aortic stenosis**. Other issues relate to its anti thrombotic behaviours and the **risk of haemorrhage**.

DOBUTAMINE / CATECHOLAMINE

Dobutamine is a **direct acting synthetic catecholamine derivative of isoprenaline**. It has primarily beta1 agonising activity although there remains some beta2 activity. It is used for **inotropic support** in **acute heart failure and cardiogenic shock** due to MI. It is also used as a **pharmacological** alternative to exercise during **stress testing** of the heart.

PHARMACEUTICAL ASPECTS

It is available as a white powder for reconstitution (250mg) or as a clear fluid for injection with 12.5mg/mL in 20ml vials. It should not be mixed with alkaline solutions due to sodium bicarbonate.

PHARMACODYNAMIC ASPECTS

Its main actions are via **direct agonism of beta1 receptors leading to increased contractility, chronotropy and myocardial oxygen demand**. Blood pressure is usually increased despite **some peripheral vasodilatation due to weak beta2 effects**. It may precipitate **tachyarrhythmias** in patients with AF or AFLUT due to increased AV conduction. It does **not effect the splanchnic or renal circulation** although there may be a slight increase in urine output secondary to CO increase.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 100%
	routes of administration IV
	doses 2.5-5mcg/kg/min uptitrate to 40mcg/kg/min max
	onset / duration 1-10 minute /10-20 minutes

DISTRIBUTION	no data
--------------	---------

METABOLISM	mechanis In tissues and hepatically to inactive metabolites
------------	---

ELIMINATION	half life 2 minutes
	excretion Urine (as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Hypertensive patients may exhibit such an exaggerated pressor response more frequently. Caution in pts with AF/AFLUT due to risk of tachycardias (digoxin may be needed). May cause ventricular ectopic activity. Increasing myocardial O2 demand may worsen ischaemia especially in setting of MI. Evidence of the development of tolerance.

DOPAMINE / NATURAL CATECHOLAMINE

Dopamine is a **natural catecholamine** which acts centrally as a neurotransmitter and peripherally it has **naturetic and diuretic properties**. When given at significantly **higher than physiological doses** it has **beta and eventually alpha adrenergic effects** including increased inotropy. It is used primarily for **improving haemodynamic parameters** and increasing urine output.

PHARMACEUTICAL ASPECTS

Dopamine is presented as clear liquid for injection in concentration of 40mg/mL in 5 mL vials. It should ideally be **administered via a central line** as extravasation may lead to necrosis. It should **not be administered with alkaline solutions** such as sodium bicarbonate.

PHARMACODYNAMIC ASPECTS

In addition to its effects on **alpha and beta receptors**, dopamine also acts via **dopamine (D_1 and D_2) receptors** via G_s and G_i coupled adenylyl cyclase leading to increased or decreased levels of cAMP. At **low doses it is a vasodilator** (due to D_1 activation) and at **high doses it demonstrates increased chronotropy, vasoconstriction then inotropy** (beta then alpha adrenergic activation).

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 100%
	routes of administration IV only
	doses commence @ 2.5 mcg/kg/min up to max 60 mcg/kg/min
	onset / duration 5 minutes / 10 minutes

DISTRIBUTION	lipid solubility does not cross the BBB
--------------	--

METABOLISM	mechanism Renal, hepatic, plasma by COMT and MAO ; 75% to inactive metabolites and 25% to noradrenaline
------------	--

ELIMINATION	half life 2 minutes
	excretion Urine (as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

It is important to **ensure adequate filling** prior to initiation of therapy. At very high doses it may cause **peripheral tissue necrosis** due to vasoconstriction. May cause **vomitting** due to chemoreceptor zone activation. **Caution** should be exhibited when patient is using **MAO inhibitors**.

Christopher Andersen 2012

ENOXAPARIN (LMWH) / ANTICOAGULANT

Consisting of **smaller fragments of heparin**, LMWH is prepared from unfractionated heparin by controlled enzymatic or chemical depolymerization. The **mean molecular weight of LMWH is 5000**, one-third the mean molecular weight of unfractionated heparin. It has similar indications to unfractionated heparin.

PHARMACEUTICAL ASPECTS

Usually given **SC**, but can be given IV for a more rapid response.

PHARMACODYNAMIC ASPECTS

Like heparin, LMWH exerts its anticoagulant activity by **activating antithrombin**. With a mean molecular weight of 5000, which corresponds to about 17 saccharide units, **at least half** of the pentasaccharide-containing chains of LMWH are **too short to bridge thrombin to antithrombin**. Consequently, LMWH **catalyzes factor Xa** inhibition by antithrombin more than thrombin inhibition

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 90% after SC injection (more than heparin) routes of administration SC (occasionally IV) doses 1mg/kg BD therapeutic, 20 or 40mg OD Prophylactic onset / duration Antifactor Xa activity: ~12 hours
DISTRIBUTION	volume of distribution 4.3 L (based on antifactor Xa activity) protein binding Does not bind to heparin binding proteins
METABOLISM	mechanism Hepatic, to lower molecular weight fragments (little activity)
ELIMINATION	half life 2-4 times longer than standard heparin, independent of dose ; excretion Urine (40% of dose; 10% as active fragments)

MAJOR ISSUES OR SIDE EFFECTS

Unlike heparin, enoxaparin is **excreted renally** and as such it requires dose adjustment in the setting of renal impairment. It has an improved side effect profile however with significantly **less thrombocytopaenia and osteoporosis**, enabling long term treatment.

ERYTHROMYCIN / MACROLIDE ANTIBIOTIC

Erythromycin is the parent drug of the macrolides, but newer drugs such as clarythromycin and roxithromycin are also available. They have a similar range of activity to penicillins and may be used as an alternative in patients with allergy. They cover most gram positive organisms, Neisseria and haemophilis, with activity against gram positive and gram negative anaerobes. They may also be used as a prokinetic in critical care.

PHARMACEUTICAL ASPECTS

Available in both oral and IV

PHARMACODYNAMIC ASPECTS

Macrolides are bactericidal or bacteriostatic depending on plasma concentration. They halt bacterial protein synthesis by binding to the 50S ribosomal subunit.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 18% to 45%
routes of administration PO/IV
doses up to 4g per day in divided doses
onset / duration 2-4 hrs to peak, food dependent

DISTRIBUTION

volume of distribution
protein binding 73% to 81%
lipid solubility minimal CSF penetration some improvement with inflamed meninges

METABOLISM

mechanism Demethylation primarily via hepatic CYP3A4

ELIMINATION

half life 1.5-2 hours
excretion Primarily feces; urine (2% to 15% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Nausea, vomiting and diarrhoea occur especially following IV delivery due to the prokinetic effect. Associated with a prolonged QT with attendant risk of arrhythmias. Actions of warfarin, theophylline and digoxin may all be increased with coadministration of macrolides.

ESMOLOL / BETA BLOCKER

Is a **cardioselective beta blocker** with **rapid onset and offset**. It is used for the short term management tachycardia and hypertension in a **monitored patient** and for SVT termination. It has no intrinsic sympathomimetic activity or membrane stabilising properties.

PHARMACEUTICAL ASPECTS

It is **only available as an IV** formulation. It is presented as a clear liquid usually at a concentration of 10mg/ml.

PHARMACODYNAMIC ASPECTS

Beta blockage leads to decreased G_s activity in receptor associated organs and associated decrease in adenylyl cyclase and intracellular Ca^{2+} . It produces decreases in heart rate and cardiac output and myocardial oxygen consumption.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability Only available as IV therefore 100% routes of admin IV dose In 10mg increments titrate to effect
DISTRIBUTION	volume of distrib 3.5 L/Kg protien binding 60% to albumin lipid solubility is high so it crosses the BBB
METABOLISM	neither hepatic or renal! by red blood cell esterases to a mostly inactive metabolite
ELIMINATION	half life 10 minutes excretetion In urine

MAJOR ISSUES OR SIDE EFFECTS

Care should be taken when used in conjunction with opioids and halothane and in patients with obstructive airway disease. Use with Ca Channel blockers may result in complete heart block. It is an **irritant to veins** and may lead to tissue necrosis with extravasation

FENTANYL / SYNTHETIC OPIOID

Fentanyl is a synthetic phenylpiperidine derivative with a rapid onset of action. It is a μ receptor agonist and as such it shares morphine's effects. Its main differences are due to its lipid solubility, rapid redistribution and prolonged context sensitive half time.

PHARMACEUTICAL ASPECTS

Fentanyl is presented as a colourless solution for injection containing 50 mcg/ml, as transdermal patches (25mcg-100mcg per hour) and as lozenges.

PHARMACODYNAMIC ASPECTS

It has the same mode of action and generally similar effects to morphine although it is less likely to precipitate histamine release.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 50-70% when taken buccal/sublingual route
routes of administration IM, IV, buccal, topical
doses Bolus: 1-2 mcg/kg or 25-100 mcg/dose; continuous infusion rate: 1-2 mcg/kg/hour or 25-200 mcg/hour
onset I.M.: 7-8 mins; I.V. immediate; Transdermal 6 hours
duration I.M.: 1-2 hours; I.V.: 0.5-1 hour; Transdermal 12 hrs

DISTRIBUTION

volume of distribution 4-6 L/kg
protein binding 80% to 85%
lipid solubility Highly lipophilic (600 times morphine)
pKa 8.4 (10% ionised)

METABOLISM

mechanism Hepatic, primarily via CYP3A4

ELIMINATION

half life I.V.: 2-4 hours, prolonged context sensitive half time
excretion Urine 75%

MAJOR ISSUES OR SIDE EFFECTS

The side effect profile is similar to morphine. Differences are due to the lipid solubility. Unlike morphine it does not cause delayed respiratory depression because it rapidly diffuses into and out of the CSF. Because of the raised context sensitive half time prolonged infusion may lead to increased duration of action and subsequent side effects.

Christopher Andersen 2012

FLECAINIDE / CLASS IC ANTIARRHYTHMIC

Flecainide is a **fluorinated derivative of procainamide**. Flecainide is used in the prophylaxis and treatment of **paroxysmal atrial fibrillation or flutter, SVT and serious ventricular arrhythmias** not responsive to other therapies including DC shock.

PHARMACEUTICAL ASPECTS

It is presented as an IV presentation in 10mg/ml or in an oral preparation in 50 or 100mg tablets. Concentration monitoring aims for a therapeutic range of 0-0.9 mg/L

PHARMACODYNAMIC ASPECTS

Flecainide **prevents the fast sodium flux** into cardiac tissue and prolongs phase 0 of the action potential. It has **no effect on the action potential duration** or the refractory period. Its effects are more pronounced in the conduction pathways. It has moderate **negative inotropic effects**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability rapidly absorbed, 90% bioavailability routes of administration IV/ PO doses IV 2mg/Kg over 10 minutes, PO 50-100mg BD
DISTRIBUTION	volume of distribution 6-10kg/L protein binding 50%
METABOLISM	mechanism hepatic with active metabolites
ELIMINATION	half life 7-22 hours , increased with congestive heart failure or renal dysfunction; End-stage renal disease: excretion Urine (80% to 90%, 10% to 50% as unchanged drug and metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Dizziness, parathesia and headaches complicate use. The major drawback of flecainide however is the **proarrhythmogenic aspects, especially in the setting of LV dysfunction or recent MI**. has significant pharmacokinetic interactions with many other drugs, including **digoxin, propranolol and amiodarone**.

FLUCLOXACILLIN/ BETALACTAM ANTIBIOTIC

Flucloxacillin is a **semi synthetic penicillin** which has a **narrow spectrum** but is useful for treating staphylococci which are **resistant** to penpen due to **beta-lactamase activity**. It is **well absorbed** from the gut but is given IV if the infection is serious. It should not be used if the organism is sensitive to penpen as penpen is more bacteriocidal.

PHARMACEUTICAL ASPECTS

May be given orally or parenterally. It is marketed under several trade names in Australia including Flopen. It is available in tablet form or powder for reconstitution.

PHARMACODYNAMIC ASPECTS

Beta-lactam antibiotics inhibit the growth of sensitive bacteria by inactivating enzymes located in the bacterial cell membrane, which are involved in the third stage of cell wall synthesis. It is during this stage that linear strands of peptidoglycan are cross-linked, beta lactams prevent this linking occurring.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 50–70%
routes of administration PO, IV or IM
doses Usually given QID or TDS in up to 2g/day

DISTRIBUTION

volume of distribution ~0.28 L/kg
protein binding up to 95%
lipid solubility penetration into CSF occurs with inflamed meninges only

METABOLISM

mechanism Hepatic with active metabolites

ELIMINATION

half life 0.75–1 hours, prolonged in anuria/renal impairment
excretion Urine (50–65% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Up to 10% of the population have allergies to penicillins. Due to the high percentage excreted renally unchanged dose adjustment is required in low urine output states. **Severe cholestatic hepatitis** has been reported idiosyncratically.

FLUMAZENIL / BENZODIAZEPINE ANTAGONIST

Flumazenil is an **imidazobenzodiazepine**. It is a **competitive antagonist** at benzodiazepine and is used for the **reversal of BDZ sedation used for anaesthesia**. It may be used for BDZ overdose or intoxication but it is rarely indicated for this use due to the associated risks of precipitating a withdrawal syndrome.

PHARMACEUTICAL ASPECTS

It is available in injectable form, 0.1mg/ml in 5ml vials.

PHARMACODYNAMIC ASPECTS

Competes with benzodiazepines at GABA_A receptors and reduces the potentiation effect of BDZ at this receptors. Flumazenil **does not antagonize** the CNS effect of drugs affecting **GABA-ergic neurons** by means **other than** the **benzodiazepine receptor** (such as ethanol, barbiturates, general anesthetics) and does not reverse the effects of opioids.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** 100%
routes of administration IV
doses 0.1-0.3mg initially, titrate to effect up to 2mg
onset / duration 1-3 mins / ~1 hour (nb may wear off prior to metabolism of the BDZ thus a **return to sedation is a concern**).

DISTRIBUTION **volume of distribution** Initial Vd: 0.5 L/kg
protein binding 40% to 50%

METABOLISM **mechanism** Hepatic; dependent upon hepatic blood flow
(therefore prolonged in liver failure)

ELIMINATION **half life** **biphasic, initial 10 mins, terminal 40-80mins**
excretion urine

MAJOR ISSUES OR SIDE EFFECTS

Side effects include nausea and vomiting. It may precipitate anxiety and agitation. Major concern is **precipitating a withdrawal syndrome** in a BDZ dependent patient, therefore caution should be exercised when considering its use.

FRUSEMIDE / LOOP DIURETIC

Frusemide is an **organism** that enter the tubular lumen primarily through **secretion into the proximal tubule**. Frusemide is a carboxylic acid derivative and represents the most potent diuretic available, are responsible for an **25% increase in the excretion of sodium filtered load**. It is used in severe heart failure to reduce peripheral and pulmonary oedema. It may also be used in chronic and acute renal failure.

PHARMACEUTICAL ASPECTS

It is available as both a tablet form in 20 and 40mg quantities and for IV injection

PHARMACODYNAMIC ASPECTS

Frusemide acts in the thick ascending limb of the loop of Henle where it inhibits Na^+ reabsorption by **blocking the $\text{Na}^+.\text{K}^+.\text{2Cl}^-$ symporter** located in the apical membrane of these cells and causing a significant diuresis. It produces **arteriolar vasodilation** which reduces TPR. **Preload is also reduced** ahead of any diuresis. In contrast to thiazides there is a decrease in renal blood flow. The main electrolyte disturbances are **hypokalaemia, hyponatraemia, hypomagnesaemia and a hypochloraemic alkalosis**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability Orally - 50% (20mg PO = 10mg IV) routes of administration PO, IV, SL, IM doses ranging from 10-20mg stat to 2-3g grams per day onset Diuresis: Oral, S.L.: 30-60 minutes; I.V.: ~5 minutes duration Oral, S.L.: 6-8 hours; I.V.: 2 hours
DISTRIBUTION	protein binding 91% to 99%; primarily to albumin
METABOLISM	mechanism Minimally hepatic
ELIMINATION	half life Normal renal function: 0.5-2 hours; End-stage renal disease: 9 hours excretion Urine (Oral: 50%, I.V.: 80% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

It may cause **ototoxicity**, especially if delivered in high doses rapidly, this is compounded by impaired renal function and the use of aminoglycosides. Electrolyte disturbances as listed above, often given **with potassium replacement** or potassium sparing drugs.

GLYCERYL TRINITRATE / ORGANIC NITRATE

Glyceryl trinitrate (also known as nitroglycerin) is an organic nitrate similar to isosorbide mononitrate and isosorbide dinitrate. It is used for the treatment of stable angina and acute pulmonary oedema.

PHARMACEUTICAL ASPECTS

It is presented in tablets for sublingual administration, in transdermal patches and as a clear liquid with a concentration of 5mg/ml. The injectable form comes in a glass vial due to GTN being absorbed into some plastics.

PHARMACODYNAMIC ASPECTS

The mode of action is the same for the inorganic nitrates although GTN must first combine with Thio containing compound to produce NO. . NO activates guanylyl cyclase in smooth muscles which in turn increases cGMP leading to a reduction in intracellular calcium and vasodilation. Venous dilation is greater than arterial dilation and the benefits in angina are believed to be related to decreased myocardial oxygen demand. In the CNS vasodilation increases ICP and causes headache. There is also relaxation of the sphincter of Oddi in the gut.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Rapidly absorbed from the sublingual mucosa and enters the circulation via the SVC. Also absorbed in the gut but first pass metabolism means a bioavailability is as low as 5%

routes of administration SL, IV, Topically

doses 400-800mcg SL, 5mg Top, 5-80mcg min uptitrated IV

onset / duration SL 1-3 mins / 25 mins. IV immediate/ 5mins

DISTRIBUTION

volume of distribution ~3 L/kg

protein binding 60%

METABOLISM

mechanism Hepatic to via thiols into NO products

ELIMINATION

half life 1-4 minutes

excretion Urine (as inactive metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Headache is a common side effect due to raised ICP from cerebral venodilation. There is rapid tolerance possibly due to thiol depletion and breaks are required for chronic administration such as transdermal delivery. A rare side effect is development of methaemoglobin.

Christopher Andersen 2012

HEPARIN / ANTICOAGULANT

Heparin is an **anionic, mucopolysaccharide, organic acid** containing many sulphide residues. It **occurs naturally** in the **liver and mast cell granules** and has a variable molecular weight of 5000 - 25000 Daltons. It is used for the treatment and prevention of VTE, ACS, and in haemodialysis and ECMO.

PHARMACEUTICAL ASPECTS

It is **derived** from **porcine mucosal cells rich in mast cells**. It is available only in injectable form (SC or IV) and is described in terms of **international units** not weight due to its variable potencies.

PHARMACODYNAMIC ASPECTS

Heparin acts as an anticoagulant by **activating antithrombin** and **accelerating the rate** at which **antithrombin inhibits clotting enzymes**, particularly **thrombin** and **factor Xa**. Once bound to antithrombin, heparin induces a conformational change in the reactive center loop of antithrombin that renders it more readily accessible to its target proteases.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability reduced SC due to endothelial binding routes of administration IV / SC doses 5000U SC BD prophylaxis, 5000U IV then infusion therapeutic doses (titrate to effect) onset / duration I.V.: Immediate; SC: ~20-30 minutes
DISTRIBUTION	protein binding very high lipid solubility low, does not cross BBB or placenta
METABOLISM	mechanism Hepatic by heparinases
ELIMINATION	half life variable half life - rapidly binds endothelial cells resulting in a short half life at low doses (30mins), as dose increases half time is prolonged (up to 150mins) excretion urine

MAJOR ISSUES OR SIDE EFFECTS

Associated with bleeding, thrombocytopenia (associated with **heparin induced thrombocytopenia syndrome HITS**) and **osteoporosis** (if delivered for greater than a month). It can cause a **transient transaminitis**. In the event of bleeding, **protamine** will bind heparin (1mg per 100U) thus reduce further haemorrhage.
Christopher Andersen 2012

HYDRALAZINE / DIRECT VASODILATOR

Hydralazine is a direct vasodilator whose mechanism of action is poorly understood. It is sometimes used intravenously in the treatment of hypertensive emergencies, and in the management of severe hypertension associated with pregnancy.

PHARMACEUTICAL ASPECTS

It is available in oral forms 25-50mg and as a 20mg powder for reconstitution and injection. It should not be reconstituted with 5% dextrose because this degrades the drug quickly.

PHARMACODYNAMIC ASPECTS

Different textbooks identify different mechanisms for this drug which indicate the poor understanding. It is possible that hydralazine activates guanylyl cyclase, increasing cAMP and decreasing Ca, causing vasodilation. NO may play a role. IP3 may be a second messenger involved. The effects are arteriole vasodilation with preserved venous tone, and minimal effect on epicardial vasculature. There is a reflex increase in HR, CO and activation of the RAAS leading to peripheral oedema.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability well absorbed but high first pass metabolism leading to a bioavailability of 30%
	routes of administration oral or IV
	doses 25-100mg BD PO, 5-10mg over 20mins, titrated
	onset / duration 15mins / up to 4 days possibly due to avid smooth muscle binding (Hemmings)
DISTRIBUTION	protein binding 85% to 90%
METABOLISM	mechanism N-acetylated in the bowel and/or the liver
ELIMINATION	half life is greatly dependent on genetically acetylation rates, ranging from 1 hour to 8 hours
	excretion

MAJOR ISSUES OR SIDE EFFECTS

The activation of the RAAS and the increase in HR and Co make this drug less efficacious. Because of this reason it is often given in combination with a thiazide or betablocker. Long term use is associated with lupus like syndrome

Christopher Andersen 2012

HYDROCHLOROTHIAZIDE / THIAZIDE DIURETIC

Thiazides are chemically **related to the sulphonamides** and are widely used in the treatment of **heart failure and hypertension**, often in combination with another class of drug. Like the loop diuretics **organic anions**. They are also mostly bound to plasma proteins, and they **gain access** to the tubule via **secretion in the proximal tubule**.

PHARMACEUTICAL ASPECTS

Is available in orange scored tablets of 25mg or in a range of different combination medications with other antihypertensives.

PHARMACODYNAMIC ASPECTS

HCT acts to inhibit Na^+ reabsorption in the early portion of the **distal tubule** by blocking the **Na^+/Cl^- symporter in the apical membrane** of these cells. **Naturesis** occurs with thiazide diuretics is **5-10% of the filtered load**. They achieve their antihypertensive effect by a **reduction in TPR** and **decrease plasma volume**, these effects are achieved at a low dose. They reduce renal blood flow and may cause a **reduction in GFR**. Like frusemide they cause **hypo-kalaemia, natraemia, chlorameic acidosis, and magneseamia**. Unlike frusemide they may cause a **hypercalcaemia secondary to decreased excretion**. Reduced glyconeogenesis and insulin may lead to **increased BSL**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	~50% to 80%
	routes of administration	PO
	doses	12.5-200mg daily
	onset / duration	Diuresis: ~2 hours / 6-12 hours

DISTRIBUTION	volume of distribution	3.6-7.8 L/kg
	protein binding	68%

METABOLISM	mechanism	Not metabolized
------------	-----------	-----------------

ELIMINATION	half life	5.6-14.8 hours
	excretion	Urine (as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

One of the main issues is **potassium derangement** in addition to the other metabolic disturbances listed above. There are a range of **indiosyncratic blood dyscrasias**. Rash and photosensitivity may occur. Interactions may **prolong** the action of **non depolarising muscle relaxants**. NSAIDs antagonise their action.

Christopher Andersen 2012

IBUPROFEN / NON SELECTIVE NSAID

Ibuprofen is a **propionic acid** non steroidal anti inflammatory drug. It has mild anti inflammatory and analgesic effects but has the **best safety profile** of the commonly used NSAIDs.

PHARMACEUTICAL ASPECTS

It is normally presented as 200mg tablets, although it may be prepared in some formulations in combination with codeine.

PHARMACODYNAMIC ASPECTS

Reversibly inhibits cyclooxygenase-1 and 2 (COX-1 and 2) enzymes, which results in decreased formation of prostaglandin precursors; has antipyretic, analgesic, and anti-inflammatory properties

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Rapid (85%)
routes of administration oral
doses 400mg TDS
onset / duration 30-60 minutes / 4-6 hours

DISTRIBUTION

volume of distribution Vd: 6.35 L
protein binding 90% to 99% (may displace highly protein bound drugs such as **warfarin** altering their pharmacodynamic properties.
pKa 4.5 **weak acid** (mostly non ionised and therefore absorbed via the gut and small bowel

METABOLISM

mechanism Hepatic via oxidation

ELIMINATION

half life 2-3 hours
excretion Urine (primarily as metabolites; 1% unchanged)

MAJOR ISSUES OR SIDE EFFECTS

Selective COX-2 inhibitors are associated with an **increased risk of thromboembolic events**, however all NSAIDs, irrespective of their selectivity can **worsen cardiovascular disease**. NSAIDs may **worsen renal function** by impairing the action of PGE_2 and causing vasoconstriction. Much of the concern with NSAIDs relates to their **increased risk of gastrointestinal events** such as ulceration and GORD. COX-2 selectivity reduces this morbidity but has not shown a mortality benefit, possibly due to the drugs causing delayed healing of ulcers. Lastly, **ibuprofen** may **reduce** the **beneficial aspects** of antiplatelet action caused by **low dose aspirin**.

ISOPRENALINE / CATECHOLAMINE

Isoprenaline is a **synthetic catecholamine** which used primarily for its **beta agonist properties**. In Australia it is indicated in **heart block, unstable bradycardia** and as an **adjunct** in cardiogenic, septic or hypovolaemic **shock**.

PHARMACEUTICAL ASPECTS

It is available in injectable form only, in concentrations of 200mcg/mL, in 1 and 5ml vials.

PHARMACODYNAMIC ASPECTS

Its effects are via agonism of the beta1 and 2 receptors. As such it **increases heart rate and inotropy (beta1)**, and **tends to maintain systolic BP but decreases diastolic BP due to decreased peripheral resistance (beta2)**. It is a potent **bronchodilator** but tends to **worsen V/Q matching** (it was previously used for this purpose in the UK but was withdrawn due to increased mortality). It has **stimulant effects on the CNS**. It **increases splanchnic and renal perfusion** due to vasodilation (beta2).

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV
doses 20mcg bolus or 0.5-10mcg/minute titrated
onset / duration IV immediate / 10-15 minutes

DISTRIBUTION

protein binding 65% protein bound

METABOLISM

mechanism Via conjugation in many tissues including **hepatic** and pulmonary

ELIMINATION

half life 2.5-5 minutes
excretion Urine (primarily as sulfate conjugates)

MAJOR ISSUES OR SIDE EFFECTS

It is contraindicated in tachycardia, and **may worsen ischaemia** due to **increased myocardial oxygen demand**. It may cause hypoxia due to a worsening of V/Q matching. Tachyphylaxis may occur in prolonged use.

KETAMINE / DISSOCIATIVE ANAESTHETIC

Ketamine is a phencyclidine (remember the street drug name PCP) derivative that produces dissociative anesthesia, which resembles a cataleptic state in which the eyes remain open with a slow nystagmic gaze. It also produces profound analgesia at subanaesthetic doses and modulates central sensitization, hyperalgesia and opioid tolerance.

PHARMACEUTICAL ASPECTS

Ketamine is presented as a racemic mixture or as the single S (+) enantiomer which is 2-3 times as potent, more quickly metabolised and has less severe side-effects than as the R (-) enantiomer. It is soluble in water forming an acidic solution pH 3.5-5.5. It comes in liquid solution, 100mg/mL in 2mL vials.

PHARMACODYNAMIC ASPECTS

Ketamine binds noncompetitively to the phencyclidine recognition site on N-methyl-D-aspartate (NMDA) receptors. Unlike propofol and etomidate, ketamine has only weak actions at GABA_A receptors. Cardio- It stimulates the SNS by increasing adrenaline and noradrenaline, this masks its mild myocardial depressant effects. Resp- The RR is often increased and it causes bronchodilation. CNS - The dissociation is between the limbic and thalamocortical regions. EEG shows alpha waves replaced by theta and beta waves. CBF and ICP are increased.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Oral: 16%; Intranasal: 50%

routes of administration IV, PO, IN

doses 1-4.5mg/kg for induction, 1-2mg/kg of analgesia

onset / duration 30 seconds / 5-10 minutes

DISTRIBUTION

volume of distribution 3 L/kg

protein binding minimal 35%

lipid solubility high lipid solubility, crosses BBB rapidly
pKa

METABOLISM

mechanism Hepatic via hydroxylation and N-demethylation
active metabolite norketamine 33% relative potency

ELIMINATION

half life Alpha: 10-15 minutes; Beta: 2.5 hours

excretion Primarily urine

MAJOR ISSUES OR SIDE EFFECTS

The main concerns with the use of ketamine are the emergence delirium which may occur as the patient comes out of anaesthesia. Cardiovascular effects may cause issues. Should be used with caution in patients at risk of elevated ICP.

Christopher Andersen 2012

LABETALOL/ BETA & ALPHA BLOCKER

Labetalol is, as the name suggests an alpha 1 blocker and a non selective beta blocker. It is used in the setting of an acute hypertensive crisis.

PHARMACEUTICAL ASPECTS

Labetalol is available as a 50-400mg tablets and as a colourless solution containing 5mg/ml. It is a racemic solution with four stereoisomers present in equal proportions. The SR isomer is likely responsible for the alpha blocking effects and the RR isomer for the betablockade.

PHARMACODYNAMIC ASPECTS

Beta blockage leads to decreased G_s activity in receptor associated organs and associated decrease in adenylyl cyclase and intracellular Ca^{2+} . It produces decreases in heart rate and cardiac output and myocardial oxygen consumption. Alpha blockage leads to decrease G_q activation and subsequent decrease in IP_3 and intracellular Ca^{2+} and subsequent peripheral vasodilation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability complete absorption but high first pass metabolism results in bioavailability 25% routes of administration IV and oral doses IV in 20mg pushes, oral for HTN 100-400mg BD
DISTRIBUTION	volume of distribution 3-16 L/kg protein binding 50% lipid solubility moderately lipid soluble, can enter CNS
METABOLISM	mechanism Hepatic, primarily via glucuronide conjugation
ELIMINATION	half life 6-8 hours excretion Urine (60% as glucuronide conjugates, <5% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Similar to other betablockers with respect to the withdrawal aspects, use in the setting of COPD and with Ca Channel blockers and Halothane. Due to its metabolism it should be used in caution in liver failure patients and elderly.

LEVOSIMENDAN / CA CHANNEL SENSITISER PHOSPHODIESTERASE INHIBITOR

Is a relatively **new agent** with **dual actions of selectively inhibiting phosphodiesterase and increasing cardiac myocyte sensitivity to calcium**. It is currently used in the short term management of severe acute heart failure.

PHARMACEUTICAL ASPECTS

It is available in IV form only 2.5mg/mL in 5 and 10ml vials.

PHARMACODYNAMIC ASPECTS

Levosimendan appears to **increase myofilament calcium sensitivity** by **binding** to cardiac **troponin C** in a calcium-dependent manner. Levosimendan also leads to **vasodilation** through the **opening of ATP-sensitive potassium channels**. By these inotropic and vasodilatory actions, levosimendan increases cardiac output without increasing myocardial oxygen demand. Levosimendan also has a selective phosphodiesterase (PDE)-III inhibitory action that may contribute to the inotropic effect of this compound under certain experimental conditions. It has been reported that levosimendan may act preferentially as a **Ca²⁺ sensitizer at lower concentrations**, whereas at **higher concentrations** its action as a **PDE-III inhibitor** becomes more prominent

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	100%
	routes of administration	IV
	doses	loading dose of 12 to 24 mcg/kg over 10 minutes then continuous infusion of 0.05-0.2 mcg/kg/min
	onset / duration	
DISTRIBUTION	volume of distribution	limited pharmacokinetic data
METABOLISM	mechanism	complete metabolism to inactive metabolites
ELIMINATION	half life	1 hour
	excretion	unknown

MAJOR ISSUES OR SIDE EFFECTS

The interference with potassium channels causes an **increase in the QTc** which is believed to result in **increased risk of arrhythmias**. Caution should be exercised in patients with renal or hepatic impairment.

Christopher Andersen 2012

LIGNOCAINE / LOCAL ANAESTHETIC

CLASS IB ANTIARRHYTHMIC

Lignocaine is an **amide local anaesthetic** with **class IB antiarrhythmic** properties. The **blocking of sodium channels** reduces nerve propagation in the PNS (and CNS) and in cardiac tissue it is used to treat ventricular arrhythmias. It has also been used for the treatment of cerebral gas embolism although this is controversial.

PHARMACEUTICAL ASPECTS

It is presented in 1% or 2% solutions (10-20mg/ml) for IM or IV injection. It is often delivered as a continuous infusion reaching steady state in around 7 hours. It may also be presented as an oral solution "xylocaine viscous"

PHARMACODYNAMIC ASPECTS

Lidocaine **blocks Na^+ channels** in cardiac muscle cells, as well as in motor and sensory nerve fibres. The **rate of rise of phase 0 of the action potential is reduced** in cardiac myocytes and the **action potential period is decreased**. In **pacemaker cells phase 4 is prolonged** due to an increased threshold potential which **reduced automaticity**.

PHARMACOKINETIC ASPECTS

ABSORPTION **routes of administration** SC, IV, IM and via ETT
doses 75–100 mg, followed by a constant infusion 2mg/min
max dose **3mg/kg or 7mg/kg with adrenaline**
onset / duration 45-90 seconds / 10-20 minutes

DISTRIBUTION **volume of distribution** 1.1-2.1 L/kg altered in CHF and liver
protein binding (duration) 60% to 80%
lipid solubility (potency) high crosses blood-brain barrier
pKa (onset of action) 7.9

METABOLISM **mechanism** 90% **hepatic**; active metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) can accumulate and may cause CNS toxicity

ELIMINATION **half life** **Biphasic**: Prolonged with CHF, liver disease, shock, ARF/CRF; **Initial: 7-30 minutes; Terminal: 2 hours**
excretion Urine (<10% as unchanged, ~90% as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Lignocaine has a **narrow therapeutic window**, with ideal concentrations <5mcg/ml for antiarrhythmic effects. Greater than 5 leads to CNS effects including confusion, sedation, agitation and paraesthesia. Greater than 20 leads to AV block, unresponsive hypotension and eventually death. See local anaesthetics page.

Christopher Andersen 2012

LISINOPRIL / ACE INHIBITOR

Lisinopril is an active drug that is not metabolised and is excreted directly into urine. It is a competitive ACE inhibitor that is used for management of hypertension, LV dysfunction post myocardial infarction and in the setting of heart failure. Its use has been shown to decrease progression of heart failure (disease modifying).

PHARMACEUTICAL ASPECTS

It is an oral formulation presented as white tablets in dosage ranging from 5mg to 20mg tablets.

PHARMACODYNAMIC ASPECTS

Cardiovascular - Competitive inhibition of angiotensin converting enzyme leads to decreased angiotensin II production and its effects. TPR and Afterload is decreased to a greater extent than preload, and this may result in improved CO in heart failure patients. HR is usually unchanged and baroreceptor reflexes also unchanged. **Renal**- the impairment of AngII means that the body is less able to respond to a drop in renal perfusion and this may precipitate failure. **Metabolic** - Accumulation of K^+ may occur due to decreased aldosterone.

PHARMACOKINETIC ASPECTS

ABSORPTION bioavailability absorbed variably with bioavailability of 30%
routes of administration oral
doses commenced at 6.25mg TDS and uptitrated
potency highly potent

DISTRIBUTION protein binding 25% protein bound

METABOLISM mechanism not metabolised

ELIMINATION half life 12 hours
excretion urine unchanged

MAJOR ISSUES OR SIDE EFFECTS

A dry cough may occur especially in patients with pre-existing lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

LOSARTAN / ANGIOTENSIN RECEPTOR BLOCKER

Losartan is a substituted imidazole compound which selectively blocks AT_2 receptors throughout the body.

PHARMACEUTICAL ASPECTS

It is presented in 50mg tablets. Unlike many of the other drugs in this class it does not come as a combination medication with a thiazide (although this combination is available overseas).

PHARMACODYNAMIC ASPECTS

Effects are broadly similar to ACE inhibitors. The blocking of AT_2 receptors reduces the action of angiotensin II. Notably as ACE is not inhibited, there is not increased levels of bradykinin, hence there is less cough associated with ARBs and possibly less vasodilation and peripheral oedema attributed to bradykinin levels.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** well absorbed from the gut but extensive first pass metabolism leads to bioavailability of 25% to 33%,
routes of administration oral
doses 50-100mg daily
onset/duration 6 hours, prolonged action due to metabolite

DISTRIBUTION **volume of distribution** 34L
protein binding high
lipid solubility low, does not cross BBB

METABOLISM **mechanism** Hepatic (14%) via CYP2C9 and 3A4 to active metabolite, E-3174 (40 times more potent than losartan)

ELIMINATION **half life** 1.5-2 hours E-3174 6-9 hours
excretion Urine (4% as unchanged drug, 6% as active

MAJOR ISSUES OR SIDE EFFECTS

Contraindicated like ACE inhibitors in bilateral renal artery stenosis, and pregnancy. Caution in sodium depleted patients similar to ACE inhibitors.

MAGNESIUM / OTHER ANTIARRHYTHMIC

is the **fourth most common cation in the body** (after Na^+ , K^+ and Ca^{2+}), and approximately 35–40% is present in cardiac and skeletal muscle. It is used in the setting of arrhythmias for **termination of VF/torsades** as per ALS protocols and in the treatment of **digitalis toxicity**. Other uses include **pre-eclampsia and eclampsia** and magnesium replacement. Off label use in **acute severe asthma**. [See syllabus notes for more Mg information]

PHARMACEUTICAL ASPECTS

It is presented in a **number of forms** including magnesium oxide, magnesium chloride and magnesium sulfate. All three are used for replacement therapy but **only magnesium sulfate is used for eclampsia and arrhythmias**. Magnesium sulfate is presented as a liquid with a concentration of 0.5mg/ml in 5 of 10ml vials.

PHARMACODYNAMIC ASPECTS

The **mechanism of action is unknown** but may reflect an effect on the inward current, possibly a Ca^{2+} current, responsible for the triggered upstroke arising from EADs. Magnesium ions are bound to cellular ATP, and act as a cofactor for Na^+/K^+ ATPase, so that intracellular concentrations of Mg^{2+} may affect Na^+ and K^+ transfer. It has **benefit even in magnesium replete patients**.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** 100% when administered IV
 routes of administration IV or PO
 doses 1-2g IV over 15 mins for torsades de pointes
 onset / duration immediate onset / duration 30 mins

DISTRIBUTION **protein binding** 30% bound to albumin

METABOLISM **mechanism** bound to bone or excreted unprocessed in urine

ELIMINATION **half life** not known
 excretion Urine (as magnesium)

MAJOR ISSUES OR SIDE EFFECTS

Care should be taken when delivering IV: **ECG monitoring, vital signs, deep tendon reflexes**; magnesium concentrations if frequent or prolonged dosing required particularly in patients with renal dysfunction, calcium, and potassium concentrations. **Contraindicated in myasthenia gravis** and **care to be taken in renal failure**.

Christopher Andersen 2012

MANNITOL/ OSMOTIC DIURETIC

Mannitol is the **only osmotic diuretic in current use**, and in contrast to other agents it commonly **produces a moderate increase in blood pressure** after administration. It is a polyhydric alcohol with a molecular weight of about 200, and is usually **synthesized** by reduction of the **monosaccharide mannose**. It is more commonly used to cause acute reductions in **intracranial pressure or intraocular pressure**. It is also used to test for **airway hyperresponsiveness**.

PHARMACEUTICAL ASPECTS

Mannitol is available in 100g in either 1000ml or 500ml (**10% or 20%**) **solutions** for injection. It **crystallises at low temperatures**, especially the 20% solution but will redissolve if heated up.

PHARMACODYNAMIC ASPECTS

As the name suggests it acts as an osmotic agent. It increases the plasma osmolality and draws water out of the CSF and vitreous body. Osmotics like mannitol are freely filtered at the glomerulus but are poorly reabsorbed. Because the proximal tubule is involved in the reabsorption of 60-70% of the filtered load this is the most important site of action.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** 100%
routes of administration IV
doses 1-2g/kg IV
onset / Diuresis: Injection: 1-3 hours; Reduction in intracranial pressure: ~15-30 minutes
duration Reduction in intracranial pressure: 1.5-6 hours

DISTRIBUTION **volume of distribution** 34.3 L; **remains confined to extracellular space generally doesn't cross BBB**

METABOLISM **mechanism** Minimally hepatic to glycogen

ELIMINATION **half life** Terminal: 4.7 hours
excretion Urine (~55% to 87% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Usually rare and idiosyncratic. It may cause symptoms of pulmonary hypertension.

MEROPENEM / CARBAPENEM

Meropenem like the other carbapenems are beta lactams that contain a fused beta-lactam ring and a five member ring system that differs from penicillins because it is unsaturated and contains a carbon atom instead of a sulphur atom. It has a broader spectrum of action than other beta lactams. Unlike the other carbapenems Meropenems do not require coadministration with cilastatin because it is not degraded by renal dipeptidase.

PHARMACEUTICAL ASPECTS

Is presented as white crystals for reconstitution. It comes in doses of 500mg or 1g and is very expensive (\$1000 per gram).

PHARMACODYNAMIC ASPECTS

Inhibits bacterial cell wall synthesis by binding to several of the penicillin-binding proteins, which in turn inhibit the final transpeptidation step of peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes (autolysins and murein hydrolases) while cell wall assembly is arrested

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability IV only 100%
doses 500mg-1g TDS
onset / duration peak at 1hr

DISTRIBUTION

volume of distribution ~0.3 L/kg
protein binding ~2%
lipid solubility crosses the BBB with CSF conc = plasma

METABOLISM

mechanism Partially metabolised Hepatic;

ELIMINATION

half life 1-1.5 hours (renal impairment increases signif.)
excretion Urine (~70% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

May cause injection site irritation. May cause seizures similar to Benpen but only in susceptible patients. Caution in renal patients due to large amount excreted unchanged. Should not be used concurrently with probenecid. Can cause confusion.

METARAMINOL - SYMPATHOMIMETIC VASOPRESSOR/

Metaraminol is a **synthetic norepinephrine** with both **direct and indirect sympathomimetic actions**. It acts mainly via **alpha1/2 adrenoceptors** to cause vasoconstriction but also has some minor beta activity. It is used in the short term **correction of blood pressure** in the setting of regional anaesthesia and off label for short term BP correction.

PHARMACEUTICAL ASPECTS

Available as a clear solution 10mg/mL in one mL vials and usually diluted to 10mg in 10ml or 20ml

PHARMACODYNAMIC ASPECTS

Its main actions are through **increased total peripheral resistance**. There may be a **transient bradycardia** due to baroreceptor feedback upon initiation of the infusion. Pulmonary vascular resistance is also increased. There may be an **increased coronary artery flow by an indirect mechanism (stimulates NA release)**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	100%
	routes of administration	IV only
	doses	given in 0.1-0.2mg boluses titrated to BP
	onset / duration	immediate / up to 20 minutes
DISTRIBUTION	volume of distribution	limited data on pharmacokinetics
METABOLISM	mechanism	Hepatic
ELIMINATION	half life	Short
	excretion	Unknown

MAJOR ISSUES OR SIDE EFFECTS

Caution should be exercised in patients with pulmonary hypertension. It may cause severe hypertension in some patients.

METHYLDOPA / CENTRAL ALPHA₂ AGONIST

Methyldopa is a centrally acting antihypertensive agent that exerts its antihypertensive action via an active metabolite. Methyldopa's significant adverse effects currently limit its use in the U.S. to treatment of hypertension in pregnancy, where it has a record for safety.

PHARMACEUTICAL ASPECTS

It is available as an oral formulation in Australia in 250mg tablets.

PHARMACODYNAMIC ASPECTS

Its metabolite produces a clonidine like alpha₂ agonist effect in cardiovascular control centres that results in reduced sympathetic outflow. The metabolite also acts as a false neurotransmitter reducing peripheral SNS effects by reducing noradrenaline synthesis. It is primarily used to depress overall SNS activity (HR, BP and TPR) but can also cause sedation, psychosis and depression.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability absorbed by an amino acid transporter (% ?) routes of administration oral doses 125-250mg BD titrated onset of action 3-6 hours, duration 24 hours (this is because of the prolonged process in substituting for noradrenaline in peripheral sites)
DISTRIBUTION	protein binding <15%
METABOLISM	mechanism Intestinal and hepatic
ELIMINATION	half life 75-80 minutes (extended in renal failure) excretion Urine (85% as metabolites) within 24 hours

MAJOR ISSUES OR SIDE EFFECTS

Sedation, decreased mental acuity and depression may occur. Dry mouth is also a problem. A small percentage of patients develop hepatotoxicity or a haemolytic anaemia.

METOPROLOL / BETA BLOCKER

Is a relatively selective beta blocker with no intrinsic sympathomimetic activity. Early use of metoprolol in haemodynamically stable myocardial infarction reduces infarct size and incidence of VF. It is used for rate control in atrial fibrillation and may be used to treat hypertension.

PHARMACEUTICAL ASPECTS

Is available in oral form as an immediate release or sustained release in increments of 25mg. It is also available as an IV formulation usually 1mg/ml

PHARMACODYNAMIC ASPECTS

Beta blockage leads to decreased G_s activity in receptor associated organs and associated decrease in adenylyl cyclase and intracellular Ca^{2+} . It produces decreases in heart rate and cardiac output and myocardial oxygen consumption. Whilst it does have some beta 2 action it has little or no effect on these receptors at doses less than 100mg.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability Absorption is rapid and complete, however there is extensive first pass metabolism bioavailability = 50% routes of admin PO or IV dose Orally in 12.5mg increments, IV in 1-2mg boluses
DISTRIBUTION	volume of distrib 5.5 L/Kg protein binding 10-20% to albumin lipid solubility is high so it crosses the BBB
METABOLISM	hepatic or renal Extensively hepatic via CYP2D6
ELIMINATION	half life 3-8hours excretion In urine 5-10% unchanged

MAJOR ISSUES OR SIDE EFFECTS

Rapid withdrawal should be avoided as it may precipitate tachycardia, hypertension and/or ischaemia. Care should be taken when used in conjunction with opioids and halothane and in patients with obstructive airway disease. Use with Ca Channel blockers may result in complete heart block

MIDAZOLAM / BENZODIAZAPIENE

Midazolam is a water-soluble benzodiazepine with an imidazole ring in its structure that accounts for its stability in aqueous solutions and its rapid metabolism. Compared with diazepam, midazolam is two to three times as potent. As with other benzodiazepines, the amnestic effects of midazolam are more potent than its sedative effects. It also has anticonvulsant properties.

PHARMACEUTICAL ASPECTS

Midazolam is presented as a clear solution at a pH of 3.5. At this pH is almost completely ionised and therefore water soluble. Since its pKa is 6.5 it is 89% un-ionised at physiological pH and can therefore cross lipid membranes.

PHARMACODYNAMIC ASPECTS

Benzodiazepines appear to produce all their pharmacologic effects by facilitating the actions of gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. Benzodiazepines do not activate GABA_A receptors but rather enhance the affinity of the receptors for GABA. As a result of this drug-induced increased affinity of GABA receptors for the inhibitory neurotransmitter, an enhanced opening of chloride gating channels results in increased chloride conductance, thus producing hyperpolarization of the postsynaptic cell membrane

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability IV 100%, PO 45%

routes of administration IV, PO, IN, IM

doses 2-2.5mg initially then 1mg boluses to effect

onset / duration 1-5 minutes / 2 hours

DISTRIBUTION

volume of distribution 0.8-2.5 L/kg

protein binding 95%

lipid solubility see above (high at physiological pH)

pKa 6.5

METABOLISM

mechanism Extensively hepatic via CYP3A4 active metab

ELIMINATION

half life 1-4 hours; prolonged with cirrhosis, congestive heart failure, obesity, and elderly

excretion Urine (as glucuronide conjugated metabolites)

MAJOR ISSUES OR SIDE EFFECTS

It uses the same cytochrome as alfentanil and if used together the effects may be prolonged. Main issues are from overdosage and excessive sedation and depression of respiratory drive.

Christopher Andersen 2012

MILRINONE / PHOSPHODIESTERASE INHIBITOR

Milrinone is a **selective phosphodiesterase inhibitor** in cardiac and vascular tissue, resulting in vasodilation and inotropic effects with little chronotropic activity. It is used in **severe refractory heart failure** for **short periods of time** and in low cardiac output states such as post cardiac surgery.

PHARMACEUTICAL ASPECTS

It is presented as a **yellow solution** containing 1mg/mL and may be stored at room temperature. It requires dilution before use and should **not** be given in the **same line as sodium bicarbonate or frusemide**.

PHARMACODYNAMIC ASPECTS

Phosphodiesterase is an intracellular enzyme which **breaks down cAMP by hydrolysis**. **Inhibitors** therefore lead to an **increase in intracellular cAMP**. Peripherally this is manifested as **arterial and venodilation** and in the myocytes this manifests as **increased contractility and therefore inotropy**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	100%
	routes of administration	IV
	doses	
	onset / duration	5-15 minutes
DISTRIBUTION	volume of distribution	0.32-0.45 L/kg
	protein binding	plasma: ~70%
METABOLISM	mechanism	Hepatic (12%)
ELIMINATION	half life	Normal renal function: ~2.5 hours
	excretion	Urine (85% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Milrinone may **precipitate or worsen SVT and VT** therefore continuous cardiac monitoring is required. They have been shown to **worsen outcome in acute on chronic heart failure**. They cause hypotension secondary to peripheral vasodilation. As the drug is excreted in urine unchanged **dose adjustment** is required in patients with **renal failure**.

MINOXIDIL/DIRECT VASODILATOR (?K ACTIVATOR)

Minoxidil is a direct vasodilator whose mechanism of action is poorly understood. It is described by Goodman as a potassium channel activator but this is contradicted in other texts. It is used primarily in severe refractory hypertension in combination with other antihypertensives.

PHARMACEUTICAL ASPECTS

It is available in 10mg tablets

PHARMACODYNAMIC ASPECTS

Similar to hydralazine in that different textbooks identify different mechanisms for this drug which indicate the poor understanding. The effects are arteriole vasodilation with preserved venous tone, and minimal effect on epicardial vasculature. There is a reflex increase in HR, CO and activation of the RAAS leading to peripheral oedema. Interestingly it is associated with increased hair production and is used topically to treat baldness.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	up to 90%
	routes of administration	oral
	doses	10-40mg PO daily
	onset / duration	~30 minutes / up to 5 days due to avid smooth muscle binding

DISTRIBUTION	protein binding	None
--------------	-----------------	------

METABOLISM	mechanism	Hepatic primarily via glucuronidation
------------	-----------	---------------------------------------

ELIMINATION	half life	4 hours
	excretion	Urine (12% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

The activation of the RAAS and the increase in HR and CO make this drug less efficacious. Because of this reason it is almost always given in combination with a thiazide or betablocker. It is contraindicated in pheochromocytoma and may precipitate pericardial effusion and worsen angina.

Christopher Andersen 2012

MORPHINE / OPIATE

Is a naturally occurring phenanthrene derivative. Along with codeine and thebaine it is isolated from opium an extract of the poppy plant *Papaver Somniferum*. Its primary use is for analgesia, it is particularly effective when treating visceral pain (so-called slow pain). It may also be used as an adjunct in the treatment of acute pulmonary oedema and rarely as an anti-tussive agent or for diarrhoea in oncology.

PHARMACEUTICAL ASPECTS

Morphine is available in a range of formulations, either as a clear liquid for injection, orally in both immediate (liquid or tablet) and sustained release forms (MS Contin).

PHARMACODYNAMIC ASPECTS

Binds primarily to G-Protein coupled μ -opioid receptors which increases adenyl cyclase and agonises their action. This has generally an inhibitory action, modulating the pain response to produce analgesia, causing dysphoria or euphoria, confusion and psychomimetic effects, depressing respiratory drive and cough reflexes, decreasing gut motility, causing reduced small bowel secretions and CBD spasm, causing urinary retention, decreasing TPR and depressing baroreceptor drive leading to postural hypotension, causing skin flushing and pruritis secondary to histamine release. Excitatory action causes miosis (parasymp)

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 30%

routes of administration oral, SC, IM, SL, IV, intrathecal

doses titrated to effect, may increase x100 with tolerance

onset / duration Oral ~30 minutes; I.V.: 5-10 minutes

DISTRIBUTION

volume of distribution 3-4 L/kg

protein binding 30% to 35%

lipid solubility low compared to other opioids

pKa 8.0 (25% ionised at pH 7.4)

METABOLISM

mechanism Metabolised to morphine-3-glucuronide (70%) and morphine-6-glucuronide (10%) by gut wall and liver . M6G is 10-20 times potent, may accumulate in renal failure

ELIMINATION

half life 2-4 hours

excretion urine and faeces

MAJOR ISSUES OR SIDE EFFECTS

Significant issues with dependence and addiction. Patients develop tolerance therefore requiring increasing doses. Significant side effects as above. If used intrathecally may develop delayed respiratory depression (rostral migration).

NALOXONE / OPIOID ANTAGONIST

Naloxone is a **pure opioid competitive antagonist** and will **reverse effects at μ , δ , and κ receptors** although its affinity is greatest for μ receptors. It is used to reverse the deleterious effects of opioid administration.

PHARMACEUTICAL ASPECTS

Naloxone is usually presented in a **1ml vial containing 400mcg**. It is also available as a minijet with the same dose but an increased volume (2 or 5ml).

PHARMACODYNAMIC ASPECTS

Naloxone competitively antagonises the opioid receptors, reversing the effects of narcotics by displacing them from the receptor. Has **minimal intrinsic activity**.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100% (IV) poorly absorbed orally
routes of administration IV / ETT/Intranasal
doses usually 400mcg bolus
onset / duration ~2 minutes / ~30-120 minutes

DISTRIBUTION

volume of distribution not known
protein binding 30%

METABOLISM

mechanism Hepatic glucuronidation to naloxone-3-glucuronide

ELIMINATION

half life 0.5-1.5 hours (nb may be less than exogenous opioid, therefore patient may become resedated when effect wears off.
excretion Urine (as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

May **precipitate SNS activity** producing hypertension, tachycardia and pulmonary oedema, Slow administration reduces risk of nausea & vomiting, **Crosses placenta and may precipitate withdrawal in opioid dependent neonate**

NEOSTIGMINE / ANTICHOLINESTERASE

Neostigmine is a **quaternary amine**. It is utilised for its **indirect cholinomimetic** properties which result from the **inhibition of cholinesterase** and therefore the reduced breakdown of acetylcholine. Clinically its most frequent use is to **reverse** the effects of **nonpolarising neuromuscular blockers**. Other indications include the treatment of **myasthenia gravis**.

PHARMACEUTICAL ASPECTS

In Australia is only available in **parenteral formulations** although overseas is also available in tablet form. When given for reversal of NMBD it is usually **coadministered** with an **anticholinergic** such as **glycopyrrolate** or **atropine** to reduce its effects at muscarinic receptors.

PHARMACODYNAMIC ASPECTS

Inhibits destruction of acetylcholine by acetylcholinesterase which facilitates transmission of impulses across myoneural junction. The **prolongs ACh actions** at the **synaptic cleft**. Cardiovascular effects include **bradycardia** (vagal potentiation), **bronchospasm** especially in asthmatics, increased **salivation**, and **intestinal motility** (which may manifest as abdominal cramping).

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability IV 100% (poorly absorbed orally)
routes of administration IV (PO in the USA)
doses **50mcg/kg** to reverse NMBD
onset / duration 1-5 mins / 1-2 hours

DISTRIBUTION

volume of distribution **low volume of distribution**
protein binding **minimally protein bound**
lipid solubility likely **low due to ionised quaternary amine**

METABOLISM

mechanism Hepatic only partial

ELIMINATION

half life 30 mins - 2hrs, **prolonged in renal disease**
excretion urine (**55% unchanged**)

MAJOR ISSUES OR SIDE EFFECTS

May lead to a cholinergic crisis with increased cholinergic effects such as increased sweating, involuntary defecation and urination, miosis, nystagmus, bradycardia, hypotension, increased muscle weakness, CNS effects including agitation, seizures and coma, respiratory depression and ultimately death.

NICORANDIL / POTASSIUM CHANNEL ACTIVATOR

Nicorandil is a potassium channel activator which also has a nitrate moiety and it is used in the treatment of stable angina

PHARMACEUTICAL ASPECTS

It is available in oral form only with 10 and 20mg tablets.

PHARMACODYNAMIC ASPECTS

Nicorandil activates KATP channels, causing hyperpolarization and relaxation of vascular smooth muscle. These effects are augmented by its nitrate moiety which is metabolised to nitric oxide which stimulates guanylyl cyclase, decreasing cAMP and causing vasodilation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	absorption is >90% and minimal first pass metabolism gives a bioavailability >80%
	routes of administration	oral
	doses	5-20mg BD
	onset / duration	30mins / up to 12 hrs
DISTRIBUTION	volume of distribution	1L/kg
	protein binding	25%
METABOLISM	mechanism	Hepatic metabolism by denitration
ELIMINATION	half life	1 hr
	excretion	In urine as inactive metabolites

MAJOR ISSUES OR SIDE EFFECTS

One of the major side effects is headaches although these usually improve with continued use.

NIFEDIPINE / Ca^{2+} CHANNEL BLOCKER

Nifedipine, is the prototypical dihydropyridine and has primarily arterial vasodilatory effects with little effect on electrical conduction in the heart. Other dihydropyridines including—amlodipine, felodipine, nifedipine, share many of the cardiovascular effects of nifedipine. It is used primarily for hypertension and angina and in the setting of preterm labour.

PHARMACEUTICAL ASPECTS

Is available in sustained and immediate release oral formulations, 10-60mg

PHARMACODYNAMIC ASPECTS

Nifedipine selectively dilates arterial resistance vessels. The decrease in arterial blood pressure elicits sympathetic reflexes, with resulting tachycardia and positive inotropy. Thus, arteriolar resistance and blood pressure are lowered, contractility and segmental ventricular function are improved, and heart rate and cardiac output are modestly increased.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability Well absorbed moderate first pass metabolism leading to bioavailability of 60%
routes of administration oral
doses 10-20mg BD
onset / duration ~20 minutes / not stated

DISTRIBUTION

protein binding ~90%
lipid solubility moderately low, minimal BBB (nimodipine is an analogue with higher solubility and is used in cerebral vasospasm)

METABOLISM

mechanism Hepatic via CYP3A4 to inactive metabolites

ELIMINATION

half life 2-5 hours (prolonged in liver failure)
excretion Urine (60% to 80% as inactive metabolites); feces

MAJOR ISSUES OR SIDE EFFECTS

It should not be used for acute blood pressure reduction in hypertensive emergencies. Peripheral oedema is a common side effect, 2-3 weeks post initiation of therapy. Other side effects are related to its vasodilating properties and include flushing, vertigo, headaches, hypotension and parathesias. There is a risk of coronary vasospasm with acute withdrawal.

SODIUM NITROPRUSSIDE / INORGANIC NITRATE

Sodium nitroprusside is an inorganic complex that acts as a prodrug. It consists of five CN groups and one NO group attached to an iron molecule covalently bonded to sodium.

PHARMACEUTICAL ASPECTS

SNP is only available in injectable form. It is unstable and must be stored out of light and not in alkaline conditions or it rapidly degrades.

PHARMACODYNAMIC ASPECTS

The nitroso group ($-N=O-$) in sodium nitroprusside reacts with sulphydryl groups ($-SH$) in vascular smooth muscle, forming nitric oxide and nitrosothiol derivatives. Both these metabolites stimulate guanylate cyclase, increasing cGMP levels and producing generalized relaxation of vascular smooth muscle. Consequently, sodium nitroprusside produces both arterial and venular dilatation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	100% (IV only)
	doses	10-200mcg/min uptitrated to effect
	onset / duration	onset <30 seconds; the peak effect 2 minutes, and the effect disappears within 3 minutes after the infusion is stopped
METABOLISM	mechanism	Nitroprusside is converted to cyanide ions in the bloodstream; decomposes to prussic acid which in the presence of sulfur donor is converted to thiocyanate (hepatic and renal rhodanase systems)
ELIMINATION	half life	Parent drug: <10 minutes; Thiocyanate: 2.7-7 days
	excretion	Urine (as thiocyanate)

MAJOR ISSUES OR SIDE EFFECTS

The main side effects are from excessive hypotension and include nausea, vomiting, abdominal pain, and postural hypotension. Abrupt withdrawal may lead to a rebound hypertension. Longer term there is significant risk of cyanide accumulation and associated toxicity and impaired oxidative phosphorylation.

Christopher Andersen 2012

NORADRENALINE/ CATECHOLAMINE

Is a naturally occurring catecholamine that is released by mammalian postganglionic sympathetic nerves. NA constitutes 10–20% of the catecholamine content of human adrenal medulla. It is used extensively in a critical care setting for maintenance of haemodynamic parameters via increase in total peripheral resistance.

PHARMACEUTICAL ASPECTS

It is presented in an injectable solution only, usually 1mg/mL in 2 mL vials and should be diluted in either 5% dextrose or 0.9% sodium chloride. It should be administered via central line due to risk of extravasation associated necrosis.

PHARMACODYNAMIC ASPECTS

Its effects are mediated mainly via stimulation of the α_1 receptors but also through beta receptors. Systemically administered NA causes peripheral vasoconstriction, increases systolic and diastolic BP and may cause a reflex bradycardia. CO may fall and myocardial oxygen usage is increased. Renal and hepatic flow fall due to vasoconstriction.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV Only
doses 8-12 mcg / minute uptitrated to effect
onset / duration immediate / 1-2 minutes

DISTRIBUTION

lipid solubility doesn't cross the BBB

METABOLISM

mechanism Via catechol-o-methyltransferase (COMT) and monoamine oxidase (MAO) Up to 25% is taken up as the drug passes through the lungs

ELIMINATION

half life 2 minutes
excretion Urine (84% to 96% as inactive metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Excessive doses cause severe hypertension. Reduced blood flow to organs such as kidney and intestines is a constant danger with the use of NE.

OXYCODONE / SEMI SYNTHETIC OPIOID

Is a semi-synthetic thebaine derivative, which has primarily μ receptor activity but also has some weak κ and δ receptor activity.

PHARMACEUTICAL ASPECTS

Presented as white tablets in either immediate release or sustained release formulations. Is presented in combination with paracetamol in US formulations.

PHARMACODYNAMIC ASPECTS

Mainly through μ receptor actions but the weak κ action may cause some of the negative effects (dysphoria, psychomimetic).

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 60% to 87%
routes of administration PO
doses 20mg oxycodone oral = 10mg morphine IV
onset / duration 10-15 minutes / 3-6 hours

DISTRIBUTION

volume of distribution 2.6 L/kg
protein binding ~45%
lipid solubility crosses BBB so high

METABOLISM

mechanism CYP3A family metabolism to noroxycodone and via CYP2D6 to oxymorphone (active), both of which are subsequently conjugated

ELIMINATION

half life 2-4 hrs
excretion urine

MAJOR ISSUES OR SIDE EFFECTS

Interindividual variability in metabolism. Other standard opioid side effects.

PARACETAMOL / UNCLASSIFIED ANALGESIC

Paracetamol is a **para-aminophenol** which is sometimes classified as a NSAID but as it has **little peripheral anti-inflammatory properties** this may be erroneous. It is used for its **antipyretic and analgesic properties**.

PHARMACEUTICAL ASPECTS

Available as a tablet or capsule usually in dosage of 500mg. Also available as a solution for titration of dose in the paediatric population and as an IV preparation.

PHARMACODYNAMIC ASPECTS

It is generally accepted that it has little effect on peripheral COX-1 or COX-2, although it **inhibits central COX-3** (a COX-1 subtype). Consequently, it **prevents** the enhanced **synthesis of prostaglandin E2** in the **hypothalamus** during pyrexia, and thus **reduces elevated body temperature**. It has similar effects to aspirin on non-specific pain. Paracetamol is also **synergistic** with opioid medications, reducing the overall opioid requirement by 20-30%.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** Primarily absorbed in **small intestine, 80%**
routes of administration PO, PR, IV
doses 1g QID or 15mg/kg QID in pts <60 kgs
onset / duration PO <1 hr / 4-6 hrs, IV 10-15mins / 4-6 hrs

DISTRIBUTION **volume of distribution** ~1 L/kg (larger than NSAIDs)
protein binding 10% less than NSAIDs
lipid solubility intermediate
pKa 9.5

METABOLISM **mechanism** Metabolised by the liver to glucuronide, sulphate and cysteine conjugates.

ELIMINATION **half life** ~2 hours -prolonged in overdose and renal dx
excretion Urine, small fraction unchanged

MAJOR ISSUES OR SIDE EFFECTS

Paracetamol has a **very safe side effect profile** and is suitable for use in pregnancy and paediatric populations. **Overdose** leads to both **hepato and renal toxicity**, plasma levels should be plotted on a nomogram and consideration of eNAC infusion commenced as appropriate. ALT is a marker of damage.

Christopher Andersen 2012

PHENOXYBENZAMINE / ALPHA BLOCKER

Phenoxybenzamine is a long acting non selective alpha blocker. It has a high affinity for alpha1 adrenoceptors. It is used in the treatment of phaeochromocytoma.

PHARMACEUTICAL ASPECTS

It is presented as capsules containing 10mg and as a clear faintly straw coloured solution for IV injection containing 100mg/2ml.

PHARMACODYNAMIC ASPECTS

Importantly it forms covalent bonds with alpha-adrenoceptors, so that the effects of single doses can last for at least several days. The restoration of normal responsiveness to alpha-adrenoceptor agonists is dependent on the synthesis of new receptors. It causes peripheral vasodilation, relaxes the urethra and increases opening of the bladder

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** is 20-30% in oral form
routes of administration oral or IV
doses 10-20mg BD, uptitrate to control BP

DISTRIBUTION **volume of distribution** not known
protein binding not known
lipid solubility not known

METABOLISM **mechanism** not known

ELIMINATION **half life** IV is 24 hours
excretion not known

MAJOR ISSUES OR SIDE EFFECTS

Orthostatic hypotension, syncope and vertigo as per other alpha blockers.

PHENYTOIN / ANTICONVULSANT

Phenytoin is a **sodium channel blocking anticonvulsant** for status epilepticus, partial or tonic clonic seizures but not absence seizures. Which is also used as a treatment for **trigeminal neuralgia** and **cardiac arrhythmias** in the setting of TCA overdose.

PHARMACEUTICAL ASPECTS

Phenytoin **poorly water soluble**, but may be presented as **fosphenytoin** which is soluble and suitable for IV preparations.

PHARMACODYNAMIC ASPECTS

The mechanism of action is dependent on the ability to bind to and **stabilise inactivated sodium channels**. This prevents the further generation of action potentials that are central to seizure activity. It may also **reduce Ca entry** into cells blocking neurotransmitter release and enhancing the action of GABA.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 90% when given orally.
routes of administration PO and IV
doses 5-20 mg/kg (**plasma levels** required aim **10-20mg/L**)
onset / duration 30mins-1hr / variable

DISTRIBUTION

volume of distribution **0.6-0.7 L/kg**
protein binding **>90%** and may have increased free plasma levels (and effects) when there is **competition for binding**.

METABOLISM

mechanism hepatic, hydroxylation and glucuronidation.
Becomes **zero order at higher concentrations**

ELIMINATION

half life **6-24 hours depending on concentration**
excretion Urine (<5% as unchanged drug); as glucuronides

MAJOR ISSUES OR SIDE EFFECTS

Side effects include **cardiac arrhythmias**, **hirsutism** in females, **gingival hyperplasia**, SIADH. It can **induce hepatic enzymes** and effect the metabolism of other drugs including warfarin. It is **teratogenic**. There is significant **interpatient variability** due to genetic predisposition to slow hydroxylation in 10% of population.

PRAZOSIN / ALPHA₁ BLOCKER

Prazosin is a highly selective alpha₁ blocker that is used for the treatment of essential hypertension, congestive heart failure, raynaud's and benign prostatic hypertrophy.

PHARMACEUTICAL ASPECTS

Prazosin is presented as 0.5 - 2mg tablets.

PHARMACODYNAMIC ASPECTS

Alpha blockage leads to decrease G_s activation and subsequent decrease in IP_3 and intracellular Ca^{2+} . Cardiovascular effects include peripheral arterial and venous vasodilation and subsequent decrease in TPR but little or no reflex tachycardia (diastole decreases the most). Urinary effects include bladder trigone and sphincter muscle relaxation which is useful in BPH (Tamulosin is also an alpha₁ blocker). CNS - syncope and headaches may occur due to rapid BP decrease.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 43% to 82% due to first pass metabolism routes of administration oral doses commenced at 0.5mg TDS then uptitrated
DISTRIBUTION	volume of distribution 0.5 L/kg protien binding 92% to 97%
METABOLISM	mechanism Extensively hepatic by demethylation and conjugation with some active metabolites
ELIMINATION	half life 2-3 hours excretion Mostly faeces, (6% to 10% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

May precipitate orthostatic hypotension, syncope or vertigo. It blunts the compensatory vasoconstriction in spinal and epidural anaesthesia and may cause profound hypotension. Dryness of mouth is also a side-effect.

PROCAINAMIDE / CLASS IA ANTIARRHYTHMIC

Is the **prototypical Vaughan Williams Class IA** antiarrhythmic which has been superseded by newer agents and is not currently available in Australia. It was **previously used in the treatment of ventricular and atrial arrhythmias**.

PHARMACEUTICAL ASPECTS

It is presented in oral and parenteral formulations for IV or IM uses.

PHARMACODYNAMIC ASPECTS

Other drugs with group 1A actions include quinidine and disopyramide. These drugs affect both atrial and ventricular arrhythmias. They **block I_{Na} , and therefore slow conduction velocity in the atria, Purkinje fibers, and ventricular cells**. At high doses they also slow AV conduction. The reduction in ventricular conduction results in **increased QRS duration** in the ECG. In addition, the 1A drugs block I_K and slow repolarization. Therefore, they **increase AP duration** and the effective refractory period (ERP) in addition to slowing conduction velocity and ectopic pacemakers. The **increase in AP duration generates an increase in QT interval**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability not stated but likely high as PO = IV doses routes of administration IV, IM, PO doses 50mg day in divided doses onset / duration I.M. 10-30 minutes
DISTRIBUTION	volume of distribution 2 L/kg protein binding 15% to 20%
METABOLISM	mechanism Hepatic via acetylation to produce N-acetyl procainamide (NAPA) (active metabolite)
ELIMINATION	half life 2.5-5.0 excretion mainly eliminated unchanged in urine

MAJOR ISSUES OR SIDE EFFECTS

Procainamide is proarrhythmogenic secondary to its **QT prolongation** and may precipitate **torsades de pointes**. If given IV it can cause **hypotension**. Chronic use is associated with development of anti nuclear antibodies and a **lupus-like syndrome**

PROPRANOLOL - BETA BLOCKER

Propranolol is a non-selective Beta Blocker with no intrinsic sympathomimetic activity. It is used to treat hypertension, angina, essential tremor, haemodynamically stable oesophageal varices and as migraine prophylaxis. It is the treatment of choice in thyrotoxicosis as it treats the effects and prevents conversion of T4 to T3.

PHARMACEUTICAL ASPECTS

Is a racemic mixture with the S-isomer conferring most effects, and the R-isomer stopping T4 to T3 conversion. It is presented in both oral and IV forms. The oral formulations may be enterically coated to ensure sustained release and range in dose from 60-160mg. Immediate release oral preparations range in dose from 10-80mg. IV formulations are significantly smaller due to extensive first pass metabolism and it is usually in 20mg/5ml preparations.

PHARMACODYNAMIC ASPECTS

Beta blockage leads to decreased G_s activity in receptor associated organs and associated decrease in adenylyl cyclase and intracellular Ca^{2+} . It produces decreases in heart rate and cardiac output and myocardial oxygen consumption.

PHARMACOKINETIC ASPECTS

ABSORPTION **bioavailability** - lipid soluble and well absorbed but has a high 1st pass metabolism leading to a bioavailability of 30%
routes of administration - oral or IV
doses PO up to 320mg, IV 0.5mg - 10mg titrated to effect

DISTRIBUTION **volume of distribution** 4 litres/kg in adults
protein binding 90% protein bound in adults
lipid solubility high lipid solubility

METABOLISM **Hepatic** via CYP2D6, and CYP1A2 to 4-hydroxypropranolol (active) and inactive compounds

ELIMINATION **half life** 3-6 hours
excretion most metabolites are excreted in urine

MAJOR ISSUES OR SIDE EFFECTS

Rapid withdrawal should be avoided as it may precipitate tachycardia, hypertension and/or ischaemia. Care should be taken when used in conjunction with opioids and halothane and in patients with obstructive airway disease.

PROPOFOL / NON BARBITURATE ANAESTHETIC

Propofol (2,6-di-isopropyl phenol) is a chemically inert phenolic derivative with anaesthetic properties. It is used for the induction and maintenance of general anaesthesia.

PHARMACEUTICAL ASPECTS

Although propofol is almost insoluble in water at pH 7.0, forming a colourless or pale straw-coloured liquid, it is highly lipid soluble. It is presented as a 1% preparation and appears as a white opaque liquid-water emulsion containing soya bean oil or purified egg phosphatide. It is a weak organic acid with a pKa of 11 and is therefore almost entirely un-ionised at physiological pH.

PHARMACODYNAMIC ASPECTS

Propofol produces general anaesthesia by selective modulation of the activity of the GABA_A receptor. The site of action is quite distinct from the modulatory site for barbiturates and benzodiazepines, and GABA itself. There is a rapid loss of consciousness due to rapid distribution across the BBB. It causes dose dependent respiratory depression and may cause apnoea. Often causes a significant drop in BP due to decreased TPR, but without a reflex tachycardia (this appears to be infusion rate dependent). It is not emetogenic and may have antiemetic properties.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV
doses 2-2.5mg/kg induction, 5mcg/kg/min uptitrated in ICU
onset / duration 30 seconds / 3-10 minutes

DISTRIBUTION

volume of distribution 2-10 L/kg; after a 10-day infusion, Vd approaches 60 L/kg; decreased in the elderly
protein binding 97% to 99%
lipid solubility is very high
pKa 11

METABOLISM

mechanism Hepatic to water-soluble sulfate and glucuronide conjugates (~50%)

ELIMINATION

half life Biphasic: Initial 40 min; Terminal 4-7 hrs (up to 60hrs)
excretion Urine (~88% as metabolites, 40% as glucuronide)

MAJOR ISSUES OR SIDE EFFECTS

It causes haemodynamic instability during induction. May be painful on injection. It may cause propofol infusion syndrome in patients on prolonged infusions (eg ICU pts) characterised by metabolic acidosis, myocardial failure and ultimately death. Monitor for lipaemia in prolonged infusion.

RAMIPRIL / ACE INHIBITOR

Ramipril is a prodrug requiring hepatic activation to ramiprilat. Ramiprilat is a competitive ACE inhibitor that is used for management of hypertension, LV dysfunction post myocardial infarction and in the setting of heart failure. It's use has been shown to decrease progression of heart failure (disease modifying).

PHARMACEUTICAL ASPECTS

It is an oral formulation presented as tablets or capsules in dosage ranging from 1.25mg to 10mg.

PHARMACODYNAMIC ASPECTS

Cardiovascular - Competitive inhibition of angiotensin converting enzyme leads to decreased angiotensin II production and its effects. TPR and Afterload is decreased to a greater extent than preload, and this may result in improved CO in heart failure patients. HR is usually unchanged and baroreceptor reflexes also unchanged. **Renal**- the impairment of AngII means that the body is less able to respond to a drop in renal perfusion and this may precipitate failure. **Metabolic** - Accumulation of K⁺ may occur due to decreased aldosterone.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 50–60% is absorbed, bioavailability 30% routes of administration oral doses commenced at 2.5 mg Daily and uptitrated potency potent
DISTRIBUTION	protein binding 75% protein bound
METABOLISM	mechanism Hepatic to the active form, ramiprilat
ELIMINATION	half life triphasic elimination profile of the active metabolite ramiprilat with T _{1/2} 1-2 hrs, 13-17hrs and >50hrs. excretion Urine (60%) and feces (40%) as parent drug and metabolites

MAJOR ISSUES OR SIDE EFFECTS

A dry cough may occur especially in patients with pre-existing lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

REMIFENTANIL / SYNTHETIC OPIOID

Is a **synthetic phenylpiperidine derivative** of fentanyl with a **unique metabolism**. It is a **pure μ receptor agonist** therefore shares many of its actions with morphine and the related compounds. It is used during anaesthesia for its potent (but short lived) analgesic properties, most commonly during larygocopy.

PHARMACEUTICAL ASPECTS

It is presented as a **white crystalline powder** for reconstitution.

PHARMACODYNAMIC ASPECTS

Pure μ receptor agonist.

NOTABLE ASPECTS

The most important aspect to the pharmacology of remifentanyl is the **rapid metabolism due to plasma and tissue esterases**. The benefit of this is that it can be used in patients with liver/renal disease, and different age, sex, body habitus without significant dose modification. It is also not context sensitive.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 100% routes of administration IV doses similar potency to fentanyl, 1mcg/kg as a bolus onset / duration 1-3 minutes
DISTRIBUTION	volume of distribution 0.1 L/kg ; increased in children protein binding ~70% (primarily α_1 acid glycoprotein) lipid solubility around 1/10 of fentanyl , but x 50 morphine pKa 7.1
METABOLISM	mechanism Rapid via blood and tissue esterases
ELIMINATION	half life Terminal: 10-20 minutes; effective: 3-10 minutes excretion Urine

MAJOR ISSUES OR SIDE EFFECTS

Bradycardia, hypotension, muscle rigidity, May contribute to **hyperalgesia** following prolonged infusion.

SODIUM VALPROATE / ANTICONVULSANT

Sodium valproate (or valproic acid) has multiple putative mechanisms and is used for the **first line treatment of epilepsy** (including tonic-clonic, partial and absence), and as a second line agent with respect to **trigeminal neuralgia, migraine** and **bipolar disorder**.

PHARMACEUTICAL ASPECTS

It is available in enteric coated tablets or an IV form. It should not be injected IM as it may cause necrosis.

PHARMACODYNAMIC ASPECTS

Proposed mechanisms of action suggested for valproate include **prolongation of sodium channels recovery phase, blocking of T-calcium channels** and **decreased breakdown of GABA**. This leads to an increased seizure threshold, and reduction in action potential propagation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability ~90% relative to I.V. dose routes of administration oral IV doses 15-30mg/kg divided doses daily up titrated onset / duration 1-4hrs
DISTRIBUTION	protein binding 80% to 90% lipid solubility high (but carrier mediated transport to the CSF may also occur)
METABOLISM	mechanism Extensively hepatic via glucuronide conjugation and mitochondrial beta-oxidation (some active metab)
ELIMINATION	half life ~15 hours excretion Urine (30% to 50% as glucuronide conjugate, 3% as unchanged drug)

MAJOR ISSUES OR SIDE EFFECTS

Nausea, cramping and vomiting occur in up to 16% of patients. A major concern is **idiosyncratic fulminant liver failure**. Monitoring of hepatic function however does not reduce the incidence of this. Monitoring of **plasma concentrations** may be required to **monitor toxicity**, but is poorly correlated to therapeutic effect.

SOTALOL / CLASS II / III ANTIARRHYTHMIC

As the name suggests, sotalol is a beta blocker but it also has class III effects and is often categorised in this class. It is used for the **prevention of SVT** and in the **treatment of ventricular tachyarrhythmias**.

PHARMACEUTICAL ASPECTS

Sotalol is a **racemic mixture** of d- and l-sotalol; **both isomers have similar Class III** antiarrhythmic effects while the **l-isomer** is responsible for virtually all of the **beta-blocking activity**. It is presented in 80 or 160mg tablets or as a clear liquid with 10mg/ml

PHARMACODYNAMIC ASPECTS

Sotalol is a nonselective β adrenergic receptor antagonist that also **prolongs cardiac action potentials** by inhibiting delayed rectifier and possibly other K^+ currents. As a result the **ventricular rate is slowed** and there is a **prolonged QT interval**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability well absorbed and up to 95% bioavailability routes of administration IV or PO doses 80-160mg PO or 50-100mg IV over 20 mins onset / duration IV ~5-10 minutes, PO 1-2 hours duration: 8-16 hours
DISTRIBUTION	volume of distribution 1.2-2.4 L/kg protein binding None
METABOLISM	mechanism None
ELIMINATION	half life 12 hours excretion Urine as unchanged drug

MAJOR ISSUES OR SIDE EFFECTS

The class III effect on the **QT interval** predisposes patients to degenerating in **torsades de pointes** (with a risk of 2% in pts with sustained VF/VT). This risk is increased in electrolyte imbalance. It **may precipitate heart failure**. Other side effects include bronchospasm, visual disturbances and sexual dysfunction.

SPIRONOLACTONE / ALDOSTERONE ANTAGONIST

Spironolactone is a competitive aldosterone antagonist and a weak androgen receptor antagonist. It is used to treat primary hyperaldosteronism (Conn's Disease) and secondary hyperaldosteronism associated oedema (such as heart failure and liver cirrhosis). The androgen blocking mechanism is utilised in women with hirsutism but causes side effects in men including gynaecomastia.

PHARMACEUTICAL ASPECTS

Presented as 25-100mg tablets.

PHARMACODYNAMIC ASPECTS

Competes with aldosterone for receptor sites in the distal renal tubules, increasing sodium chloride and water excretion while conserving potassium and hydrogen ions. Blocks androgen receptors sites weakly.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability incompletely absorbed routes of administration oral doses 25-200mg daily onset / duration 3-4 hours / up to 3 days
DISTRIBUTION	volume of distribution protein binding 91% to 98% lipid solubility
METABOLISM	mechanism Hepatic to multiple metabolites, including active metabolites canrenone and 7-alpha-spirolactone
ELIMINATION	half life Spironolactone: 1-2hrs metabolites up to 24hrs excretion Urine and feces

MAJOR ISSUES OR SIDE EFFECTS

As this medication is potassium sparing, elevated potassium is a significant risk and should be monitored. It is often given in combination with a loop diuretic for this reason. The androgen blocking aspects mean gynaecomastia and galactorrhea are a problem for men taking spironolactone and it is not suitable in pregnancy.

TRAMADOL / SYNTHETIC OPIOID

Tramadol is a **cyclohexanol derivative**. It is a **racemic mixture**, with each enantiomer producing specific actions.

PHARMACEUTICAL ASPECTS

Tramadol is presented as immediate release, 12 hour release and 24 hour release tablets.

PHARMACODYNAMIC ASPECTS

Tramadol has **agonist properties at all opioid receptors** but particularly at μ receptors. At equi-analgesic doses it produces less respiratory depression and constipation. In other aspects it is similar to morphine. It also **inhibits the reuptake of noradrenaline and serotonin**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability 75% routes of administration oral doses has 1/5th potency of morphine , 50-100mg q4-6hr onset / duration ~1 hour / 9 hours (immediate release)
DISTRIBUTION	volume of distribution 2.5-3 L/kg protein binding ~20% lipid solubility crosses BBB
METABOLISM	mechanism Extensively hepatic via demethylation , glucuronidation, and sulfation; active metabolite formed by CYP2D6 (M1; O-desmethyl tramadol)
ELIMINATION	half life Tramadol: ~6-8 hours; Active metabolite: 7-9 hours; prolonged in elderly, hepatic or renal impairment excretion Urine (30% unchanged drug; 60% as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

Caution should be exercised when used in **combination with SSRIs or MAO inhibitors** as it may precipitate a serotonin syndrome. As noted above it causes **less respiratory depression and constipation**, but these remain significant side effects especially in combination with other agents. Patients **deficient in CYP2D6** may have a **decreased analgesic** effect.

THIOPENTONE (THIOPENTAL) / BARBITURATE

Thiopental is 5-ethyl-5'-(1-methylbutyl)-2-thiobarbituric acid and is the sulphur analogue of pentobarbital. It is a short-acting barbiturate with sedative, hypnotic, and anticonvulsant properties. Apart from induction it is also used in status epilepticus.

PHARMACEUTICAL ASPECTS

The sodium salt is a pale yellowish-white powder with a bitter taste and an garlic-like odour. It readily dissolves in deionized water producing an alkaline solution due to its ionized sulphur atom (S⁻), which has strongly basic properties and attracts H⁺. Once reconstituted it is stable for ~ one week.

PHARMACODYNAMIC ASPECTS

Thiopental and other barbiturates mainly act by increasing the duration of GABA-dependent chloride channel opening. Barbiturates depress the sensory cortex, decrease motor activity, alter cerebellar function, and produce drowsiness, sedation, and hypnosis. In high doses, maximally reduces brain O₂ consumption- and exhibits anticonvulsant activity; barbiturates produce dose-dependent respiratory depression.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailability 100%
routes of administration IV
doses 3-5mg/kg as induction dose
onset / duration I.V.: 30-60 seconds / 5-30 minutes

DISTRIBUTION

volume of distribution ~1.6 L/kg
protein binding 72% to 86%
lipid solubility high lipid solubility
pKa 7.6

METABOLISM

mechanism Hepatic, primarily to inactive metabolites, when given as an infusion may develop zero order kinetics due to enzyme saturation

ELIMINATION

half life 3-11.5 hours
excretion renal, reduce dose by one quarter when CrCl <10

MAJOR ISSUES OR SIDE EFFECTS

Due to a dose dependent reduction in CO, SV and TPR may cause a reflex tachycardia. Respiratory depression is dose dependent. Decreased CBF, ICP, and brain O₂ consumption. Severe anaphylaxis in 1 in 20000. May precipitate acute porphyria.

TIROFIBAN / GLYCOPROTIEN IIb/IIIa ANTAGONIST

Tirofiban binds to the glycoprotein IIb/IIIa receptor on the surface of platelets. It has a similar action to the monoclonal antibody abciximab. It is used in patients with non stable angina and NSTEMI in high risk patients.

PHARMACEUTICAL ASPECTS

It is presented for injection in 0.25mg/ml in 50ml vials. Its trade name is aggrastat. It is usually given with low dose aspirin and heparin infusion. All markers of coagulation should be checked within six hours of commencing treatment, and then daily.

PHARMACODYNAMIC ASPECTS

Tirofiban and abciximab act by inhibiting the platelet glycoprotein IIb/IIIa receptor and as such they block the final common pathway of platelet aggregation. They do not block platelet adhesion, secretion of platelet products, inflammatory effects or thrombin activation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability routes of administration doses onset / duration
------------	--

more rapid offset than abciximab and other agents.

DISTRIBUTION	volume of distribution protein binding
--------------	---

METABOLISM	mechanism
------------	-----------

ELIMINATION	half life excretion
-------------	------------------------

65% renal and 25% faecal clearance

MAJOR ISSUES OR SIDE EFFECTS

Requires dose adjustment in renal failure with creatinine clearance <30ml/min. Side effects relate to haemorrhage, although spontaneous haemorrhage is uncommon. Reversal is problematic and platelet infusion is recommended if there is uncontrolled bleeding.

VANCOMYCIN / GLYCOPEPTIDE

Vancomycin is a tricyclic glycopeptide antibiotic produced by *Streptococcus orientalis*. It possesses a broad spectrum of activity against gram positive bacteria including MRSA.

PHARMACEUTICAL ASPECTS

Recommended to be stored at 2-8 degrees. Available as a clear solution. It may cause vessel irritation when infused peripherally and it is recommended that it is given slowly as a result. Monitoring is required to ensure adequate dosing.

PHARMACODYNAMIC ASPECTS

Vancomycin exerts its action by inhibiting the formation of the peptidoglycan polymers of the bacterial cell wall. Unlike penicillins, which act mainly to prevent the cross-linking of peptidoglycans which gives the cell wall its strength, "vancomycin" prevents the transfer and addition of the muramylpentapeptide building blocks that make up the peptidoglycan molecule itself.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability Oral: Poor; I.M.: Erratic; Intraperitoneal: ~38% routes of administration IV doses 500mg-1g QID is the usual dose onset / duration
DISTRIBUTION	volume of distribution Vd: 0.4-1 L/kg; Distributes widely in body tissue and fluids, except for CSF, improved CSF penetration with inflamed meninges protein binding ~50%
METABOLISM	mechanism Little or no metabolism
ELIMINATION	half life Biphasic half life, prolonged in renal fail. excretion via kidneys unchanged

MAJOR ISSUES OR SIDE EFFECTS

May cause hypersensitivity reactions including anaphylaxis. Rapid infusion is associated with red-man syndrome. Ototoxicity which appears to be related to dose is a concern. Nephrotoxicity has declined with improved formulations.

VASOPRESSIN / VASOPRESSOR / ADH

Vasopressin is a **naturally occurring peptide released from the posterior pituitary** also known as **anti diuretic hormone**. It is available in two forms for therapeutic use, desmopressin (DDAVP) and vasopressin. It is used in **diabetes insipidus**, control of bleeding in patients with **VwB disease and mild haemophilia** and off label as a **catecholamine sparing drug** in the setting of mild to moderate septic shock.

PHARMACEUTICAL ASPECTS

It is measured in international units and comes in a vial with 20 units per mL requiring dilution for effective delivery. It cannot be given orally as it is inactivated by trypsin.

PHARMACODYNAMIC ASPECTS

Vasopressin receptors are GPCR that exist in **three main forms, V1a, V1b and V2**. **V1a** receptors are found in multiple places including **vascular smooth muscle** and platelets are responsible for the **vasopressor actions** and platelet aggregation. **V2** receptors are found renal collecting duct and ascending limb, and are responsible for **ADH actions**.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	100% IV
	routes of administration	IV (off label), IM, SC, IN
	doses	I.V.: 0.01-0.04 units/minute for the treatment of septic shock.
	onset / duration	rapid / 2-8 hrs if given IN
DISTRIBUTION	volume of distribution	limited data
METABOLISM	mechanism	hepatic and renal
ELIMINATION	half life	if given intranasally 4 hours
	excretion	Urine (5% unchanged)

MAJOR ISSUES OR SIDE EFFECTS

Causes **hyponatraemia with water retention** avoid in CHF. May cause severe **vasoconstriction and necrosis** (not to be given peripherally). Doses above 0.04 units/min may cause **arrhythmias or asystole**. Actions on GI smooth muscle cause **abdominal cramping, nausea and diarrhoea**.

VERAPAMIL / Ca^{2+} CHANNEL BLOCKER

Verapamil is a synthetic derivative of papaverine that is supplied as a racemic mixture. It is the levoisomer of verapamil which is specific for slow calcium channels. It is used to control hypertension, treat angina, and in arrhythmias such as SVT to slow conduction through the SA and AV nodes.

PHARMACEUTICAL ASPECTS

It is available as immediate and sustained release oral formulations in doses ranging from 40-240mg. It may come in combination with the ACE inhibitor trandolapril. It is also available as an IV formulation with a concentration of 2.5mg/ml (2ml vial).

PHARMACODYNAMIC ASPECTS

The levoisomer causes main effects (arterial vasodilation). Verapamil slows conduction through the AV and SA node to a greater extent than other Ca channel blockers. The dextroisomer of verapamil is devoid of activity at slow calcium channels and instead acts on fast sodium channels, accounting for the local anesthetic effects of verapamil (1.6 times as potent as procaine).

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailability	Well absorbed by high first pass metabolism leading to bioavailability of 20% to 35%
	routes of administration	oral or IV
	doses	
	onset / duration	1-2 hours / 6-8 hours (for oral intake)
DISTRIBUTION	volume of distribution	3.89 L/kg
	protein binding	~90%
METABOLISM	mechanism	Hepatic via multiple CYP isoenzymes, one active metabolite with 20% activity
ELIMINATION	half life	3-7 hours
	excretion	Urine (70% as metabolites, 3% to 4% as unchanged drug); feces (16%)

MAJOR ISSUES OR SIDE EFFECTS

in patients without congestive heart failure, ventricular performance is not impaired and actually may improve, especially if ischemia limits performance. In contrast, in patients with congestive heart failure, intravenous verapamil can cause a marked decrease in contractility and left ventricular function. It should be avoided in pts with WPW.

Christopher Andersen 2012

WARFARIN / ORAL ANTICOAGULANT

Warfarin is a **water soluble coumarin derivative** and is used for the prophylaxis of systemic thrombo embolism in patients with AF, valvular heart disease and in the prevention of VTE and PE.

PHARMACEUTICAL ASPECTS

Warfarin is a **racemic mixture** of two enantiomers R and S with the biological effects more prominent in the S isomer. It is presented as oral tablets in a range of dosages and requires careful **titration according to INR** in all patients.

PHARMACODYNAMIC ASPECTS

Warfarin inhibits vitamin K epoxide reductase (VKOR), thereby **blocking the γ -carboxylation** process of **clotting factors II, VII, IX and X** and the **anticlotting Protien C and S**. This results in the synthesis of vitamin K-dependent clotting proteins that are only partially γ -carboxylated. Warfarin acts as an anticoagulant because these **partially γ -carboxylated proteins have reduced or absent biologic activity**. The onset of action of warfarin is delayed until the newly synthesized clotting factors with reduced activity gradually replace their fully active counterparts.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty oral, rapid complete routes of administration oral doses titrate to PT/INR onset / duration 24-72 hrs / Full therapeutic effect: 5-7 days
DISTRIBUTION	volume of distribution 0.12 L/kg protien binding 99%
METABOLISM	mechanism Hepatic, primarily via CYP2C9 two common variants in this cytochrome lead to increased warfarin effect (therefore decreased dosing requirement)
ELIMINATION	half life 20-60 hours; Mean: 40 hours excretion Urine (92%, primarily as metabolites)

MAJOR ISSUES OR SIDE EFFECTS

The main side effect of warfarin is **bleeding**. In the setting of uncontrolled haemorrhage vitamin K may be given along with FFP in accordance with the INR. Other side effects include **idosyncratic skin necrosis**. There are extensive interactions with other **meds, diet and protien binding**. May cause a **prothrombotic** state during initiation due to **Protien C ad S being blocked first**.

Christopher Andersen 2012