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 alkanisation. It is mainly used for the treatment of glaucoma and altitude sickness and may be used as an adjunct in epilepsy (increased CO2 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	bioavailabilty	~100%
	routes of administration	oral (IV also possible)
	doses	glaucoma 250mg q6hr
	onset / duration	
DISTRIBUTION	lipid solubility	crosses BBB
	protien binding	highly protien 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 alkanisation. Contraindicated in patients with acidosis, may worsen sodium and potassium depletion. Can cause parathesias, fatigue, drowsiness, depression, n+v, abdopain.

Christopher Andersen 2012

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 paroxsmal SVT. It is also used sometimes for slowing rapid atrial arrhythmias to aid diganosis.

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	bioavailabilty 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.

Christopher Andersen 2012

ADRENALINE/ CATECHOLAMINE

Is a naturally occuring catecholamine that is released the adrenal medulla. It is used in a critical care setting for maintenence 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 adrengeric 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 stabilses mast cells which is why it is used in acute anaphlyaxis.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty 100% routes of administration IV, IM, SC, Inhaled, ETT doses 1mg in arrest, 0.1mg in anaplaxis, 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.

Christopher Andersen 2012

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 t1/2 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	bioavailabilty 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

Christopher Andersen 2012

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 protien synthesis by binding to the bacterial 30S ribosomal subunit.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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
	protien binding	<30%
	lipid solubility	low lipid solubility - reduces gut absorption
		some CSF penetration with inflammed meniges (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 otoxicity. May cause C.Diff overgrowth. They decrease the prejunctional release of acteylcholine, which reduces post junctional sensitivity to acetlycholine and therefore increases NDMR activity and cause muscle weakness.

Christopher Andersen 2012

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 is 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	bioavailabilty 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) protien 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 hyperthroidism (1%). Hepatic - it is associated with cirrhosis, hepatitis and jaundice. LFT monitoring is recommended. Ophthalmic - corneal microdeposits occur commonly but usually resolve of cessation. Cardiac - it is not particularly arrhythmogenic despite QT prolongation (likely because of it 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 are may be given with clauvanic acid.

PHARMACEUTICAL ASPECTS

May be given orally or parenterally, however amoxycillin is preferred orally due to its improved oral bioavailability. It is marketted 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 occuring.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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
	protien 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 impair
	excretion	Urine (90% as unchanged drug) within 24 hours

MAJOR ISSUES OR SIDE EFFECTS

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

Christopher Andersen 2012

ASPIRIN / IRREVERSIBLE NONSELECTIVE NSAID

Aspirin (acetylsalicylic acid) is a non selective non steroidal antinflammatory drug which is used for its analgesic, anti inflammatory and its irrevesible 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

bioavailabilty 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;
protien 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 occuring tertiary amine derived from the belladona plant. It's 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 or 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	bioavailabilty 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 protien 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 overdosage of atropine may cause a central anticholinergic syndrome characterised by excitement, hallucinations and hyperpyrexia. In overdosage this leads to coma, respiratory depression and death.

Christopher Andersen 2012

BENZYLPENICILLIN / BETALACTAM ANTIBIOTIC

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

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 occuring.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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
	protien 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 penicllins. 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

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. It's 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 coverting 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	bioavailabilty rapidly absorbed, bioavailability of 60-70% routes of administration oral doses commenced at 6.25mg TDS and uptitrated potency moderately potent
DISTRIBUTION	protien binding 25% protien bound
METABOLISM	mechanism oxidised in the liver and coverted 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-exisiting lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

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	bioavailabilty	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
	protien binding	85-95%, may lead to non linear dose dependent responses
	lipid solubility	crosses the BBB regardless of meingeal 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".

Christopher Andersen 2012

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	bioavailabilty 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 protien binding 20% to 40% lipid solubility 10% CSF penetration (up to 40% with inflammed meniges)
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, vomitting and abdominal pain. Caution in epileptic patients as it may cause seizures, confusion and restlessness. Some issues with anaphalaxis.

Christopher Andersen 2012

CLONIDINE / CENTRAL ALPHA$_2$ 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 opiods and for the diagnosis of phaechromocytoma.

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 anxigenic at higher doses. Provides analgesia without respiratory centre depression and is synergistic with opiods. Renal - inhibition of ADH may be the cause of diuresis. Endocrine-stress response to surgery inhibited. Insulin release in reduced, usually BSL ok.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty 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 protien 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 glycoprotien IIb/IIIa receptor transforming into its active form.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty Well absorbed routes of administration oral doses 300mg loading, 75mg daily onset / duration 2hrs / 5 days
DISTRIBUTION	volume of distribution protien 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 neutropaenia.

Christopher Andersen 2012

DEXMEDETOMIDINE / CENTRAL ALPHA$_2$ AGONIST

Is a central alpha2 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 alpha1:alpha2 ratio of 1:1600.

PHARMACEUTICAL ASPECTS

Medetomidine is a racemic misture 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 alpha2 adrenoceptors in the locus cerrulus. Peripheral alpha2b-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

bioavailabilty IV therefore 100%
routes of administration IV
doses Usually 1mcg/kg over 20 minutes, then a mainte nence dose of 0.2-0.7 mcg/kg per hour titrated
onset of action I.V. Bolus: 5-10 minutes

DISTRIBUTION

volume of distribution Vss: ~118 L
protien 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.

Christopher Andersen 2012

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 in 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

bioavailabilty 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
protien 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 excereted 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_D 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 vomitting, 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 / Ca^{2+} 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

bioavailabilty 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
protien 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.

Christopher Andersen 2012

DIPYRIDAMOLE / PLATELET PDE INHIBITOR

Dipyridamole acts by inhibiting phophodiesterase, 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 phophodiesterase 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	bioavailabilty	variable depending on concurrent oral intake
	routes of administration	IV and oral
	doses	200mg BD for CVA prevention
	onset / duration	onset is within 1hr, 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 glucoronides 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.

Christopher Andersen 2012

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 reconsititution (250mg) or as a clear fluid for injection with 12.5mg/mL in 20ml vials. It should not be mixed with alkaline solutions due or 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 tachyarrythmias 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	bioavailabilty 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 tachcardias (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.

Christopher Andersen 2012

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	bioavailabilty	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	bioavailabilty 90% after SC injection (more than heparin) routes of administration SC (occasionaly 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) protien 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.

Christopher Andersen 2012

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	bioavailabilty 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 conjuction with opiods 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

Christopher Andersen 2012

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 morphines effects. It's main differences are due to it's 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

bioavailabilty 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
protien 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

FLUCLOXACILLIN/ BETALACTAM ANTIBIOTIC

Flucloxacillin is a semi synthetic penicillin which has a narrow spectrum but is useful for treating staphlococci which are resistant to benpen 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 benpen as benpen 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 occuring.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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
	protien 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 impair
	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.

Christopher Andersen 2012

FRUSEMIDE / LOOP DIURETIC

Frusemide is an organis ion 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 chronci 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 $Na^+.K^+.2Cl^-$ 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, hypomagnesmaemia and a hypochloraemic alkalosis.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty 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	protien 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 liste above, often given with potassium replacement or potassium sparing drugs.

Christopher Andersen 2012

GLYCERYL TRINITRATE / ORGANIC NITRATE

Glyceryl trinitrate (also known as nitrogylcerin) 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 tern 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	bioavailabilty Rapidly absorbed from the sublingual mucosa and enters the circulation via the SVC. Also absorbed in the gut but first pass metabolism means a bioavailabity 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 protien 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, mucoploysaccaride, 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 haemodylasis 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	bioavailabilty 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	protien 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 ot 150mins) excretion urine

MAJOR ISSUES OR SIDE EFFECTS

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

Christopher Andersen 2012

ISOPRENALINE / CATECHOLAMINE

Isoprenaline is a synthetic catcholamine 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 of 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 splanchic and renal perfusion due to vasodilation (beta2).

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty 100% routes of administration IV doses 20mcg bolus or 0.5-10mcg/minute titrated onset / duration IV immediate / 10-15 minutes
DISTRIBUTION	protien binding 65% protien 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. Tachyphlaxis may occur in prolonged use.

Christopher Andersen 2012

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 norad, this masks its mild myocardial depressent effects. Resp- The RR is often increased and it causes bronchodilation. CNS - The dissociation is between the limbic and thalmocortical regions. EEG shows alpha waves replaced by theta and beta waves. CBF and ICP are increased.

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailabilty 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
protien 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 anaethesia. 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 hypertenisve 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	bioavailabilty 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 protien 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.

Christopher Andersen 2012

LEVOSIMENDAN / CA CHANNEL SENSITISER PHOSPHODIESTERASE INHIBITOR

Is a relatively new agent with dual actions of selectively inhibiting phsophodiesterase and increasing cardiac myoctye 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	bioavailabilty	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 interferrence with potassium channels causes an increase in the QTc which is believed to result in increased risk of arrhythmias. Caution should be exercised in paitents with renal or hepatic impairment.

Christopher Andersen 2012

LIGNOCAINE / LOCAL ANAESTHETIC CLASS IB ANTIARRHYTHMIC

Lignocaine is an amide local anaesthetic with has 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 contraversial.

PHARMACEUTICAL ASPECTS

It is presented in 1% or 2% solutions (10-20mg/ml) for IM or IV injection. It is often delivered as a continuos 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
protien 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 monoethylg lycinexylidide (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 antiarrythmic effects. Greater than 5 leads to CNS effects including confusion, sedation, agitation and parathesia. Greater than 20 leads to AV block, unresponsive hypotension and eventually death. See local anaesthetics page.

Christopher Andersen 2012

LISINOPRIL / ACE INHIBITOR

Lisonpril 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. It's 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 coverting 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	bioavailabilty absorbed variably with bioavailabilty of 30% routes of administration oral doses commenced at 6.25mg TDS and uptitrated potency highly potent
DISTRIBUTION	protien binding 25% protien 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-exisiting lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

Christopher Andersen 2012

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 Ca2+ 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	bioavailabilty 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	protien 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 introccular 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 it heated up.

PHARMACODYNAMIC ASPECTS

As the name suggests it acts as an osmotic agent. It increased 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	bioavailabilty 100% routes of administration IV doses 1-2g/kg IV onset / Diuresis: Injection: 1-3 hours; Reduction in intracra nial 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 idosyncratic. It may cause symptoms of pulmonary hypertension.

Christopher Andersen 2012

MEROPENEM / CARBAPENEM

Meropenem like the other carbepenems are beta lactams that contain a fused beta-lactam rung 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 carbepenems Meropenems do not require coadministration with cilastatin because it is not degrade 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	bioavailabilty	IV only 100%
	doses	500mg-1g TDS
	onset / duration	peak at 1hr
DISTRIBUTION	volume of distribution	~0.3 L/kg
	protien binding	~2%
	lipid solubility	crosses the BBB with CSF conc = plasma
METABOLISM	mechanism	Patrially 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 concurrenly with probenecid. Can cause confusion.

Christopher Andersen 2012

METOPROLOL / BETA BLOCKER

Is a relatively seletive 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	bioavailabilty Absoption is rapid and complete, however there is extenisve 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 protien 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 excretetion 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 conjuction with opiods and halothane and in patients with obstructive airway disease. Use with Ca Channel blockers may result in complete heart block

Christopher Andersen 2012

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	bioavailabilty	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
	protien 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 is 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	bioavailabilty	100%
	routes of administration	IV
	doses	
	onset / duration	5-15 minutes
DISTRIBUTION	volume of distribution	0.32-0.45 L/kg
	protien 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 continuos 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.

Christopher Andersen 2012

MORPHINE / OPIATE

Is a naturally occuring phenanthrene derivative. Along with codiene and thebain 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-Protien coupled μ-opioid receptors which increases andenylyl cyclase and agonises their action. This has generally an inhibitory action, modulating the pain response to produce analgesia, causing dyphoria 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

bioavailabilty 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
protien 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).

Christopher Andersen 2012

NICORANDIL / POTASSIUM CHANNEL ACTIVATOR

Nicorandil is a potassium channel activator which also has a nitrate moiety and it is used in the treatment of stabel 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 sugmented by its nitrate moiety which is metabolised to nitric oxide which stimulates guanylyl cyclase, decreasing cAMP and causing vasodilation.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty absorption is >90% and minimal first past 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 protien 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.

Christopher Andersen 2012

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, nicardipine, 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

bioavailabilty 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

protien 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.

Christopher Andersen 2012

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 a 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	bioavailabilty 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, vomitting, 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 occuring 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 maintenence 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 adminstered via central line due to risk of extravasation associated necrosis.

PHARMACODYNAMIC ASPECTS

Its effects are mediated mainly via stimulation of the alpha1 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 usuage is increased. Renal and hepatic flow fall due to vasoconstriction.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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.

Christopher Andersen 2012

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 mu receptor actions but he weak K action may cause some of the negative effects (dysphoria, psychomimetic).

PHARMACOKINETIC ASPECTS

ABSORPTION

bioavailabilty 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
protien 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.

Christopher Andersen 2012

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 eroneous. 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	bioavailabilty 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) protien binding 10% less than NSAIDs lipid solubiltiy intermediate pKa 9.5
METABOLISM	mechanism Metobolised by the liver to glucuronide, sulphate and cysteine conjugates.
ELIMINATION	half life ~2 hours -prolonged in overdosage 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. Overdosage 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

PROPANOLOL - BETA BLOCKER

Propanolol is a non-selective Beta Blocker with no intrinsic sympathomimetic activity. It is used to treat hypertension, angina, essential tremor, haemodynamically stable oesophaegeal varacies 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	bioavailabilty - 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 protien binding 90% protien 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 conjuction with opiods and halothane and in patients with obstructive airway disease.

Christopher Andersen 2012

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 maintenence 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 a 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 protien binding 97% to 99% lipid solubility is very high pKa 11
METABOLISM	mechanism Hepatic to water-soluble sulfate and glucuron ide 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.

Christopher Andersen 2012

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 coverting 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	bioavailabilty 50–60% is absorbed, bioavailability 30% routes of administration oral doses commenced at 2.5 mg Daily and uptitrated potency potent
DISTRIBUTION	protien binding 75% protien 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-exisiting lung disease. Caution should be exercised in patients on potassium sparing medications. NSAIDs may precipitate renal failure.

Christopher Andersen 2012

REMIFENTANIL / SYNTHETIC OPIOID

Is a synthetic phenylpiperdine derivative of fentanil 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 aneasthesia for its potent (but short lived) analgesic properties, most commonly during larygoscopy.

PHARMACEUTICAL ASPECTS

It is presented as a white crystalline powder for reconstitution.

PHARMACODYNAMIC ASPECTS

Pure mu receptor agonist.

NOTABLE ASPECTS

The most important aspect to the pharmacology of remifentanil 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 modicification. It is also not context sensitive.

PHARMACOKINETIC ASPECTS

ABSORPTION	bioavailabilty	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
	protien binding	~70% (primarily alpha1 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.

Christopher Andersen 2012

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 b 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	bioavailabilty 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 protien 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.

Christopher Andersen 2012

SPIRONOLACTONE / ALDOSTERONE ANTAGONIST

Spionolactone 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 utiised 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

bioavailabilty incompletely absorbed
routes of administration oral
doses 25-200mg daily
onset / duration 3-4 hours / up to 3 days

DISTRIBUTION

volume of distribution
protien 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 andogren blocking aspects mean gynaecomastia and galactorrhea are a problem for men taking spirolonactone and it is not suitable in pregnancy.

Christopher Andersen 2012

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

bioavailabilty 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
protien 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.

Christopher Andersen 2012

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

bioavailabilty 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
protien 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.

Christopher Andersen 2012

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	bioavailabilty	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
	protien 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.

Christopher Andersen 2012

VASOPRESSIN / VASOPRESSOR / ADH

Vasopressin a naturally occuring peptide released from the posterior pituitary also known as anti diuretic hormone. It is available in two forms for theraputic use, desmopressin (DDAVP) and vasopressin. It is used in diabetes insipidis, control of bleeding in patients with VwB disease and mild haemophilia and off label as a catecholamine sparing drug in the 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 GCPR 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	bioavailabilty 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.

Christopher Andersen 2012

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 arrythmias 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 then 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	bioavailabilty	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
	protien 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 avaioded 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 cytochome 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 uncrontrolled 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