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Drugs used in CCU

1. Introduction

People with life-threatening injuries and illnesses need critical care. Critical care involves close, constant attention by a team of specially-trained health professionals. It usually takes place in an intensive care unit (ICU) or trauma center. Problems that might need critical care treatment include complications from surgery, accidents, infections and severe breathing problems. Monitors, intravenous tubes, feeding tubes, catheters, ventilators and other equipment are common in critical care units. These can sustain life but can also increase the risk of infection. Similarly the use of life saving drugs is also most important for the client in times of emergency.

Since the advent of coronary care units (CCU), the hospital mortality from ventricular fibrillation has fallen. This is due not only to rapid defibrillation with direct current shock but also to the treatment of arrhythmias likely to predispose to ventricular fibrillation. However, the constant cardiac monitoring, leading as it does to early treatment with anti-arrhythmic medication, will naturally expose patients to drugs they may not otherwise have received.Common drugs would include: ace inhibitors, beta blockers, calcium channel blockers, direct vasodilators (most common one on our floor is hydralazine), amiodarone, glycosides, nitrates, opioids, electrolyte replacements, insulin and other hypoglycemics, as well as other drugs for their co morbidities.

2. Classification of drugs

Pharmacological Classification

Grouping of drug according to their pharmacological action or of most important constituent or their therapeutic use is termed as pharmacological or therapeutic classification of drug. This classification is more relevant and is mostly followed method. Drugs like digitalis, squill and strophanthus having cardiotonic action are grouped together irrespective of their parts used or phylogenetic relationship or the nature of phytoconstituents they contain. Some of the commonly used drugs are listed as follows.

- Analgesics (opiods,NSAIDs,adjuvants)
- Antibiotics
- Antithrombotics (anticoagulants,antiplatelets, thrombolytics)
- Neuromuscular-blocking agents
- Recombinant activated protein C (is a recombinant form of human activated protein C that has anti-thrombotic, anti-inflammatory, and profibrinolytic properties)
- Sedatives
- Stress ulcer prevention drugs
- Vasopressors
- Intravenous fluids
- Inotropes

- **Cardiac inotropes**

An **inotrope** is an agent that alters the force or energy of muscular contractions. Negatively inotropic agents weaken the force of muscular contractions. Positively inotropic agents increase the strength of muscular contraction.

The term *inotropic state* is most commonly used in reference to various drugs that affect the strength of contraction of heart muscle (myocardial contractility). However, it can also refer to pathological conditions. For example, ventricular hypertrophy can increase inotropic state, whereas dead heart muscle (myocardial infarction) can decrease it.

Both positive and negative inotropes are used in the management of various cardiovascular conditions. The choice of agent depends largely on specific pharmacological effects of individual agents with respect to the condition. One of the most important factors affecting inotropic state is the level of calcium in the cytoplasm of the muscle cell. Positive inotropes usually increase this level, while negative inotropes decrease it. However, not all drugs involve calcium release, and, among those that do, the mechanism for manipulating the calcium level can vary from drug to drug.

Positive inotropic agents

Positive inotropic agents increase myocardial contractility, and are used to support cardiac function in conditions such as decompensatedcongestive heart failure, cardiogenic shock, septic shock, myocardial infarction, cardiomyopathy, etc.

Examples of positive inotropic agents include:

- Berberine
- Bipyridine derivatives
    - Inamrinone
    - Milrinone
- Calcium
- Calcium sensitisers
    - Levosimendan
- Catecholamines
    - Dopamine
    - Dobutamine
    - Dopexamine
    - Epinephrine (adrenaline)
    - Isoprenaline (isoproterenol)
    - Norepinephrine (noradrenaline)
- Digoxin
- Eicosanoids
    -
    - Prostaglandins
- Phosphodiesterase inhibitors

    - Enoximone
    - Milrinone
    - Theophylline
- Glucagon

Negative inotropic agents

Negative inotropic agents decrease myocardial contractility, and are used to decrease cardiac workload in conditions such as angina. While negative inotropism may precipitate or exacerbate heart failure, certain beta blockers (e.g. carvedilol, bisoprolol and metoprolol) have been shown to reduce morbidity and mortality in congestive heart failure. Cardiac glycosides

- Beta blockers
- Calcium channel blockers
    - Diltiazem
    - Verapamil
    - Clevidipine

Class IA antiarrhythmics such as

- Quinidine
- Procainamide
- disopyramide

Class IC antiarrhythmics such as

- Flecainide

ACE inhibitors

Mode of action

- Block bradykinin kinase as well as ACE and increase the concentration of bradykinin
- Do not cause reflex tachycardia.

Clinical uses

- Hypertension. Particularly effective in renovascular hypertension but also effective in anephric patients and in low renin hypertension.
- Chronic heart failure results in improved prognosis as well as improved symptom control
- Post MI in all patients who have had pulmonary edema in association with MI, however transient.

Contraindications

- Bilateral renal artery stenosis or stenosis in a solitary kidney

Example: Captopril

- Contains as sulphydryl group that interacts with Zn^{2+} of ACE binding site with greater affinity than angiotensin I
- Given sublingually has an onset of action in 20-30 min with maximum effect after approx 50 min and duration of action of about 4 h
- Adverse effects include agranulocytosis, Stevens-Johnson syndrome.

Classification

Class I - membrane stabilizers

Depress depolarization of cardiac cell membrane by restricting entry of fast sodium current resulting in reduction in the maximum rate of rise of phase 0 of the action potential. This leads to slower rate of conduction, increased threshold for excitation and prolongation of the effective refractory period. It also reduce rate of phase 4 diastolic depolarization, at doses which have no other effects, causing a reduction in spontaneous automaticity.
- class I drugs further subdivided by their effect on the duration of the action potential

Quinidine (Class Ia)

Mechanism of action

- decrease maximum rate of rise of phase 0

- depresses spontaneous phase 4 depolarization in automatic cells (results in prolonged QT)
- in general slows conduction through atrial, ventricular and Purkinje fibres causing QRS prolongation but usually has no effect on sinus rate or R interval - antivagal action may accelerate AVN conduction

Pharmacokinetics

Administration: PO - absorption rapid and almost complete. SR preparations available but their bioavailability may be lower than that of the standard formulation Never given IV as may cause severe hypotension and myocardial depression

Distribution: peak plasma concentrations at 2-3 hrs. 80% bound to albumin. Volume of distribution reduced in cardiac failure resulting in higher plasma levels which may lead to toxicity

Clinical uses

Limited by lack of IV preparation to prophylaxis after cardioversion or after acute administration of lignocaine. Effectively maintains sinus rhythm after cardioversion from AF but mortality is increased.

-Effective against both atrial and ventricular arrhythmias. However enhanced AV conduction may result in dangerously increased ventricular rates in atrial fibrillation or flutter and pre-

treatment with digoxin must thus be given prior to any attempt to convert these arrhythmias with quinidine.

-Use should probably be restricted to patients with life-threatening arrhythmias in whom quinidine has been "proven" to be effective

Adverse effects

- High plasma levels cause myocardial depression, vasodilatation and hypotension
- sinus arrest

- AV dissociation

- QT prolongation and hence torsades de pointes. All type 1a drugs associated with risk of torsades but quinidine appears to be the worst offender

- Nausea, vomiting and diarrhoea are common

- Cinchonism: headaches, tinnitus, partial deafness, disturbed vision and nausea

- Hypersensitivity reactions: fever, purpura, thrombocytopaenia, hepatic dysfunction

- May cause haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase deficiency

Drug interactions

- Diuretic induce hypokalaemia can produce life-threatening arrhythmias in patients on drugs which prolong QT interval. Characteristic arrhythmia is VT

- May increase serum digoxin levels

- Cimetidine and some beta blockers reduce hepatic blood flow and may cause toxic concentrations
- concentrations decreased by hepatic enzyme inducers (eg phenytoin , phenobarbitone)

Disopyramide (Class Ia and III)

Mode of action

- similar to quinidine

- increases atrial abolishes ectopic & refractory period, re-entrant atrial

- decreases sinus node arrhythmias refractory period

- anti-cholinergic effect. Antagonizes vagal actions and may be useful in suppressing supra-ventricular arrhythmias

- slows conduction in accessory pathway and sometimes prolongs His-Purkinje refractory period, although it has little effect on PR, QT, or QRS duration

- some Ca blocking effects

Pharmacokinetics

Administration: PO/IV. Following MI patients achieve lower plasma levels after oral dose. **Distribution:** peak levels within 2 hrs. 25% plasma protein bound but binding saturable and depends both on disopyramide and metabolite concentrations - contributes to its unusual pharmacokinetic property of higher renal clearance at higher plasma levels. Volume of distribution decreases following MI

Clinical uses

- AV nodal, AV re-entry and ventricular arrhythmias. Should not be used to treat AF or atrial flutter without prior control of ventricular rate with beta blockers or verapamil
- useful in preventing paroxysms of AF

Adverse effects

Cardiac
- myocardial depression; may be clinically important. Related both to plasma levels and rate of administration. Contra-indicated in heart failure, severe LV dysfunction
- prolongs QT -predisposes to re-entrant VT and especially torsades de pointes
- sinus node depression

Other
-Anticholinergic activity may lead to urinary retention, dry mouth, blurred vision etc
- may precipitate glaucoma

Lignocaine (Class Ib anti-arrhythmic)

Also has local anaesthetic actions)

Pharmacokinetics

Admininistration: IV

Distribution: volume of distribution 1.5 l/kg in normals, 0.5 l/kg in heart failure
Clinical use

- first line drug for VT after acute MI and cardiac surgery

Adverse effects

- high concentrations may cause bradycardia, hypotension and even asystole

- Negative inotrope

- in 10% of patients may induce ventricular arrhythmias

- GI upset with nausea and vomiting

- CNS: parasthesiae, twitching and generalized tonic-clonic seizures

Injection rate may be important in precipitating toxic reactions, which are also related to free drug concentration, which is particularly determined by the concentration of acute phase protein alpha-1 acid glycoprotein. Latter increases after MI so that although long-term infusions may lead to increasing total lignocaine concentrations the free drug level may remain fairly constant.

- crosses placenta rapidly but information on its use in pregnancy is limited. No reports of teratogenicity

Drug interactions

- hepatic clearance reduced in patients receiving cimetidine, propranolol or halothane

Flecainide (Class Ic)

Mode of action

- depresses phase 0 and slows conduction throughout the heart

- delays repolarization in (canine) vnetricular muscle with significant prolongation of intracardiac monophasic action potential

- causes concentration related increase in PR, QRS and intra-atrial conduction intervals and prolongs effective ventricular refractory period

- sinus node function may also be affected particularly in patients with intrinsic sinus node disease

Pharmacokinetics

- admin: PO/IV; well absorbed with peak plasma concentrations after 3 hrs

Clinical use

- life-threatening tachyarrhythmias: supra-ventricular or ventricular

- most effective drug at blocking conduction by anomalous pathways

Adverse effects

- up to 30% of patients

- -ve inotrope: exacerbation of CCF

- proarrhythmic effects: more common in patients with severe underlying cardiac dysfunction and more malignant arrhythmias. Torsades may occur even in patients without structural heart disease

- dizziness

- visual disturbance eg blurring

- headache

- nausea

- tremor

- diarrhea

- conduction blocks including bundle branch block, complete heart block

- sinus arrest

- increase in pacing thresholds

- increased difficulty in cardioversion of tachyarrhythmias

Class II - beta blockers

Competitive antagonists and also block possible arrhythmogenic effect ofcAMP

- Decrease potential for arrhythmias to develop in response to catecholamines

- eg bretylium: blocks release of sympathetic transmitters

-Indirect blockade of Ca channel opening by attenuating adrenergic activation

Sotalol (Class III (& II)

Mode of action

- prolongs action potential duration in atria, ventricles, AVN and accessory AV pathways
- potent non-cardioselective beta blocker

- antifibrillatory actions which are superior to those of conventional beta blockers

Pharmacokinetics

- admin: IV/PO

Clinical use

- SVT: less effective than adenosine and verapamil in treatment of AVNRT and AVRT. Will prevent recurrence.

- AF & atrial flutter: probably ineffective as chemical cardiovertor but effective in preventing recurrence after cardioversion

- VT: as safe and more effective than lignocaine to terminate sustained VT when given IV.

Dose

- dose required to prolong cardiac repolarisation higher than that required to cause beta blockade
- IV dose: 0.5-1.5 mg/kg over 5-20 min

- PO: start at 80 mg bd and increase to 160 mg bd

Adverse effects

- adverse effects of beta blockers. Negative inotropic effect of beta blockade slightly offset by weak positive inotropism due to prolongation of action potential, allowing more time for calcium influx into myocardial cells

- QT prolongation

- crosses placenta readily. Fetal bradycardia, hypoglycaemia, hyperbilirubinaemia and intrauterine growth retardation are concerns. Most reports have not shown significant adverse fetal effects but beta-blockers are probably best avoided in known intrauterine growth retardation

Class III- K channel blockers

Prolong duration of action potential with resulting prolongation of effective refractory period- eg amiodarone, sotalol, disopyramide, bretylium

Amiodarone

Mode of action

- class III anti-arrhythmic with weak class I, II (b blocker) and class IV actions
- prolongs effective refractory period of myocardial cells, AV node and anomalous pathways
- depresses automaticity of SA and AVN
- may also be a non-competitive blocker of a and b receptors
- haemodynamic effects: coronary vasodilator (direct effect on smooth muscle, Ca channel blockade, and a blockade), peripheral vasodilator, negative inotrope

Pharmacokinetics

Administration: IV/PO.

Distribution: enormous apparent volume of distribution (70 l/kg). Stored in fat and other tissues. $T_{1/2}$ after multiple dosing of 54 days

Elimination: metabolized in liver and excreted via biliary and intestinal tracts

Clinical uses

- effective against most tachyarrhythmias
- patients with poor LV function or patients with frequent ventricular ectopics post MI although did reduce "arrhythmia deaths"

Adverse effects

- bradycardia, heart block and proarrhythmic effects. Latter are mild compared to other anti-arrhythmics
- congestive cardiac failure (2-3%)
- hypotension (28% following IV administration. Not dose related)
- increases defibrillation threshold
- corneal microdeposits which cause visual haloes and photophohia. Dose related and resolve when drug discontinued
- hyperthyroidism, hypothyroidism, interference with thyroid function tests

- photosensitivity
- eosinophilic lung infiltration (early, fever, SOB, cough)
- pulmonary fibrosis
- hepatitis
- tremor, ataxia, peripheral neuropathy, fatigue, weakness. Usually occur during loading. Dose related
- skin discolouration

Drug interactions

- displaces digoxin from binding sites and, more importantly, interferes with elimination
- inhibits warfarin metabolism
- b blockers and Ca antagonists augment the depressant effect of amiodarone on SA and AVN function as well as negative inotropic effects
- raises quinidine and phenytoin concentrations

Bretylium (Class III)

Mode of action

- increases action potential duration and refractory period of cardiac cells

- antifibrillatory effect on ventricular muscle - may be more important than class III effects in emergency treatment of malignant ventricular arrhythmias

- initially causes noradrenaline release and then produces the equivalent of a sympathectomy, preventing noradrenaline release (class II effect)

Clinical use

- useful adjunct to DC shock in managing life-threatening ventricular arrhythmias, especially refractory VF

Dose

5mg/kg IV over 15-20 min but in an emergency often given over 1-2 min

Adverse effects

Postural hypotension most significant side effect. Nausea and vomiting possible

Class IV- calcium channel blockers

- Inhibit slow inward calcium mediated current and depress phase 2 and 3

- Slow SAN pacemaker cells and AVN conduction by direct blockade of Ca channels

- Have inportant effects on upper and middle parts of the AV node

Site of action-SAN, atrium

Beta-blockers

Anti-arrhythmic properties appear to be a class effect with no one drug being intrinsically superior

Mode of action

- reduce slope of phase 4 in pacemaker cells thus prolonging their refractoriness

- slow conduction in AVN

- refractoriness and conduction in the His-Purkinje system are unchanged

Clinical use

- most effective in arrhythmias associated with increased cardiac adrenergic stimulation (eg TTX, phaeochromocytoma, exercise or emotion)

- SVT: may terminate re-entry tachycardias when the AVN is part of the re-entry circuit but less effective than adenosine or verapamil. Slow ventricular response to other SVTs
- VT: generally ineffective for the emergency treatment of sustained VT.

Adverse effects

- Cross placenta readily. Fetal bradycardia, hypoglycaemia, hyperbilirubinaemia and intrauterine growth retardation are concerns. Most reports have not shown significant adverse fetal effects but beta-blockers are probably best avoided in known intrauterine growth retardation.

Labetalol (alpha-1 and non-selective beta blocker)

- beta blockade predominates during IV administration

- beta blockade prevents reflex increase in heart rate, cardiac output and myocardial oxygen consumption
- in pre-eclampsia rapidly reduces BP without decreasing uteroplacental blood flow
- crosses placenta but neonatal bradycardia and hypoglycaemia rarely seen
- disadvantages in pre-eclampsia include interpatient variability in dose requirement and variable duration of action

Dose

For acute hypertension

- bolus of 1-2 mg/kg over 10 min
- OR mini-boluses of 20 mg followed by 20-80 mg every 10 min
- OR incremental infusion of 0.5-4 mg /min. This method is least likely to cause hypotension and bradycardia

For pre-eclampsia

- 10 mg IV initially
- double dose every 10 min as necessary to a maximum of 300 mg
- alternatively: 1-2 mg/min IVI reducing to 0.5 mg/min or less after arterial pressure is controlled

- ***Mannitol***

Haemodynamic and antiviscosity effects

- decreases the viscosity of blood (not only by decreasing haematocrit, but by decreasing the volume, rigidity, and cohesiveness of RBC membranes thereby decreasing the mechanical resistance to passage through the microvasculature)

- also decreases systemic vascular resistance, mild positive inotropic effect on the heart

- net effect is an increase in CO and oxygen delivery

Pharmacokinetics

-there is relatively little information on the pharmacokinetics of mannitol infusions

Uses of mannitol in neurocritical care

- ICP lowering effect is rapid, usually appearing within minutes, although the maximal effect may not be seen for 20-40 minutes or more.
- Decrease in the ICP depend on the compliance at the time
- Different CNS pathological conditions produce different patterns of change in volume dynamics and intracranial compliance because of the differential effects on the cardinal components of the intracranial space: parenchyma (~80%), cerebral blood volume (~10%), and CSF (~10%).

Haemorrheologic Effects

- can be achieved using an infusion

- may avoid some of the adverse haemodynamic effects

- relatively contraindicated in those with impaired renal function

Adverse effects

Acute adverse haemodynamic effects

- variable effects on BP following a bolus of mannitol

- a slight increase in pulse pressure and MAP is most commonly observed, but transient decreases in BP secondary to decreases in SVR are not uncommon.

- the acute vasodilatory effect of mannitol is not well understood and may be due to the following

- decrease in plasma pH
- release of ANP
- histamine release from basophils
- direct impairment of contractile properties of vascular smooth muscle

- acute mannitol induced hypotension is not frequently a serious clinical problem when given slowly over 15 to 30 minutes.

- precipitation of acute heart failure is not common and is rarely observed in those with impaired renal function

➢ Antibacterials

Minimum inhibitory concentration: the minimum concentration of drug that completely inhibits bacterial growth.

Mode of action

Action is dependent on selective toxicity ie the drug is toxic but only to target organismsexploit the differences between human cells and those of bacteria. The most striking difference is that bacteria have cell walls as well as a cell membrane while human cells only have a cell membrane. The cell wall is the principal target of blactam antibiotics. The other principal targets are intracellular. As a result the effectiveness of those antibiotics which act at these sites is dependent on their ability to penetrate the cell. Aminoglycosides, for example, have to be actively transported across the bacterial cell membrane. Glycoproteins (eg vancomycin, teicoplanin) are unable to penetrate the outer membrane of gram-negative organisms and thus have restricted activity against these organismsprecise sequence of events leading to death of bacteria still the subject of research

Families of antimicrobials

- Aminoglycosides
- Beta-lactams
- Fluoroquinolones
- Glycopeptides
- Lincosamides
- Macrolides
- Streptogramins

➢ **Neuromuscular-blocking agents**

These drugs fall into two groups:

- **Non-depolarizing blocking agents**: These agents constitute the majority of the clinically-relevant neuromuscular blockers. They act by competitively blocking the binding of ACh to its receptors, and in some cases, they also directly block the ionotropic activity of the ACh receptors.

- **Depolarizing blocking agents**: These agents act by depolarizing the plasma membrane of the skeletal muscle fiber. This persistent depolarization makes the muscle fiber resistant to further stimulation by ACh.

Non-depolarizing blocking agents

A **neuromuscular nondepolarizing agent** is a form of neuromuscular blocker which do not depolarize the motor end plate.

Depolarizing blocking agents

A **neuromuscular depolarizing blocking agent** is a form of neuromuscular blocker which will depolarize the motor end plate.

An example is succinylcholine.

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to acetylcholine. However, these agents are more resistant to degradation by acetylcholinesterase, the enzyme responsible for degrading acetylcholine, and can thus more persistently depolarize the muscle fibers. This differs from acetylcholine, which is rapidly degraded and only transiently depolarizes the muscle.

There are two phases to the depolarizing block. During phase I (*depolarizing phase*), they cause muscular fasciculations (muscle twitches) while they are depolarizing the muscle

fibers. Eventually, after sufficient depolarization has occurred, phase II (*desensitizing phase*) sets in and the muscle is no longer responsive to acetylcholine released by the motoneurons. At this point, full neuromuscular block has been achieved.

The prototypical depolarizing blocking drug is succinylcholine (suxamethonium). It is the only such drug used clinically. It has a rapid onset (30 seconds) but very short duration of action (5–10 minutes) because of hydrolysis by various cholinesterases (such as butyrylcholinesterase in the blood). Succinylcholine was originally known as diacetylcholine because structurally it is composed of two acetylcholine molecules joined with a methyl group. Decamethonium is sometimes, but rarely, used in clinical practice.

- **Anti-fibrinolytics**

Eg: Tranexamic acid

- include ε aminocaproic acid, tranexamic acid and aprotonin
- reduce breakdown of blood clots
- appear to decrease bleeding after cardiac surgery
    - use of aprotonin is associated with a higher mortality compared to ε aminocaproic acid and tranexamic acid
- reduce rebleeding and death after GI bleeding, but role in relation to endoscopic therapy and proton pump inhibitors is unknown
- complications include thrombosis and possible increased risk of death with aprotonin

- **Anti-fungals**

Mode of action

- inhibit ß-(1,3) glucan synthesis, damaging fungal cell walls
- no drug target in mammalian cells

Spectrum of activity

- rapidly fungicidal against most *Candida* spp.
- fungistatic against *Aspergillus* spp.
- active against cyst form of *Pneumocystis carinii*. Probably only useful for prophylaxis.

Caspafungin

Pharmacokinetics

- administration: IV
- 96% plasma protein bound
- predominantly hepatic metabolism (hydrolysis and N-acetylation). Hepatic uptake slow, leading to long terminal half-life of ~10.6 h

    - reduce dose to 50% of daily dose in patients with severe hepatic dysfunction, but give usual loading dose
    - also adrenal and splenic metabolism
    - plasma concentrations slightly increased in renal failure (unrelated to renal excretion or plasma protein binding
    - cannot be dialysed
- distribution: urinary concentration low, CSF concentration expected to be low

Clinical use

- as effective and less toxic than amphotericin B in patients with invasive candidiasis or candidaemia
    - insufficient data in patients with endocarditis, persistent infection with neutropaenia, ophthalmitis, mediastinitis, meningitis or urinary tract infection
    - some suggestion that in *C. parapsilosis* infection response may be slower to caspofungin than to amphotericin
- invasive aspergillosis

Adverse effects

- fever (~35% of patients)
- hepatotoxicity
    - raised transaminases common in patients receiving caspofungin but may not be attributable to caspofungin
    - hepatic necrosis in animals given large doses (5-8 mg/kg)
- headache in ~15%
- phlebitis in ~20%
- rash infrequent
- haemolysis may occur but clinically significant haemolysis is rare

Drug interactions

- slight increases in clearance with co-adminstration of:
    - phenytoin
    - carbamazepine
    - dexamethasone
    - efavirenz, nelfinavir, nevirapine
- rifampicin - concentrations of both drugs increased
- tacrolimus - concentration of tacrolimus decreased by ~20%
- cyclosporin - increased caspofungin plasma concentration

- **Antithrombotics (anticoagulants,antiplatelets, thrombolytics)**

Anti-platelet agents

<u>Aspirin</u>

Pharmacodynamics

- irreversibly acetylates and inactivates cyclo-oxygenase: enzyme responsible for conversion of membrane arachidonic acid to prostaglandin endoperoxides and thromboxane A2
- platelets lack nuclear machinery to replenish enzyme so platelets are affected for their lifespan
- platelet release inhibited and platelet aggregation impaired

Ticlopidine (Clopidogrel)

- Thioenopyridine platelet inhibitor
- Prodrug. Requires activation by cytochrome P450 in liver
- Irreversibly modifies platelet ADP receptor and thus blocks pro-aggregatory effects of ADP

Pharmacokinetics

- Administration: PO. Almost completely absorbed
- Platelet inhibition reaches a maximum after 5-8 days of repeated doses
- 50-60% of oral dose eliminated in urine, remainder in faeces

Clinical uses

Unclear. Appears to be more effective than aspirin in preventing stroke in patients who have already had a stroke or a TIA. However aspirin remain treatment of choice because of ticlopidine's bone marrow suppressant effects.

Ticlopidine plus aspirin is more effective than aspirin alone or aspirin plus anticoagulants in preventing thromboembolic complications related to coronary stenting, but it is not licensed for this use.

Adverse effects

- Neutropaenia in 2.4%, severe in 0.8%
- TTP in 0.02%
- Nausea, diarrhoea.
- Rashes
- Abnormal liver function tests rarely. Cholestatic jaundice has been reported
- Rashes and diarrhoea are more common than with aspirin but other GI effects, including peptic ulceration are less common.

Contraindications

- history of leucopaenia, thrombocytopaenia or agranulocytosis
- blood diseases that prolong bleeding time
- lesions likely to bleed (eg active peptic ulcer, acute haemorrhagic stroke)

- caution in patients with impaired liver function. Should be discontinued if hepatitis or jaundice develops. There is little experience of its use in patients with renal impairment

Similar to ticlopidine in that it is also a thioenopyridine platelet inhibitor and requires activation by cyctochrome P450. Same mode of action

Pharmacokinetics

- Administration: PO. After repeated oral doses >50% is absorbed.
- Inhibition of platelet function reaches a maximum after 3-7 days
- Elimination: 50% of a single oral dose is excreted in the urine and 46% in faeces

Clinical uses

Unclear. Appears to offer little or no worthwhile advantage over aspirin. Little data to support its use in combination with aspirin instead of ticlopidine combined with aspirin.

Adverse effects

- rash (severe rash more common than with aspirin)
- GI haemorrhage (severe haemorrhage less common than with aspirin)
- diarrhoea, upper GI symptoms, neutropaenia, intracranial haemorrhage (similar incidence to aspirin)

Contraindications

- Severe liver impairment
- Active bleeding
- Breast feeding women
- In first few days following acute myocardial infarction
- Manufacturer does not recommend its use in unstable angina, in those undergoing PTCA or CABG.
- Should be used with caution in patients who may be at risk of increased bleeding and should be stopped 7 days prior to surgery if anti-platelet effect is not desired.
- Use with caution in patients with renal or hepatic impairment.

Mode of action

- specifically target one of two surface structures of influenza virus, the neuraminidase protein
- neuraminidase enables the virus to emerge from the host cell and form new viruses. By inhibiting neuraminidase, these agents prevent the virus from spreading to other cells.

➢ **Anti-virals**

Oseltamivir

Pharmacokinetics

- orally administered
- high bioavailability (90%)
- undergoes hepatic metabolism to the active carboxylate
- oseltamivir carboxylate
    - 3% protein bound
    - renally excreted with an elimination half life of 6-10 hours. The dose should be halved in patients with creatinine clearance <30 ml/min
        - in vitro data suggest that a daily maintenance dose (mg) of 0.52-1.27 times the ultrafiltration rate (ml/min) should be adequate.
- Current guidelines for influenza A/H5N1 recommend that oseltamivir should be administered within 48 hours at a dose of 75mg twice daily for five days in adults, with weight adjusted doses for children. In more severe cases higher doses and a longer course of therapy has been recommended. The efficacy of neuramidase inhibitors diminishes substantially if administered after 60 hours of infection and efficacy suboptimal when instituted later in the course of illness.

- **Calcium antagonists**

Nifedipine

Mechanism of action

- inhibits slow inward calcium mediated current with resultant slight negative inotropic effect and decreased arterial and venous smooth muscle tone.

Clinical uses

- angina especially Prinzmetal. Should not be used without a beta blocker in unstable angina as reflex tachycardia may result in worsening angina or infarction.

- hypertension including pre-ecplampsia. Does not decrease uterine perfusion nor cause fetal deterioration
- mild achalasia in patients unfit for surgery

- oesophageal spasm

Pharmacokinetics

- admin: PO/SL. Slow releases preparation available.

- distrib: peak concentration 1-2 hours after oral admin. 90% plasma protein bound.
- plasma half-life: 4-5 hours but duration of effect may be 8-12 hours
- elim: metabolised in the liver to inactive metabolites

Adverse effects

- small risk of heart failure

- worsening angina/cerebral ischaemia in some

- headache 6%

- nausea, flushing, dizziness - tolerance usually develops in 1-2 weeks

- ankle oedema due to increased proximal capillary pressure due to dilatation of resistance vessels. Does not usually respond to diuretics

- in hypertensive patients already receiving beta blockers for angina may produce severe hypotension without improving angina

- similar effect sometimes seen in early days after MI

- hepatitis and glucose intolerance rare

- relaxes uterine muscle. May increase risk of post-partum haemorrhage

Drug interactions

- beta blockers as above

- exaggerated hypotensive response may occur when used with magnesium due to latter's Ca blocking effects

Dose

- for pre-eclampsia: 10 mg SL/PO, repeated if necessary after 30 min. BP usually reduced after 10-20 min and duration of action 3-4 h

Amlodipine, Nicardipine

- pure arteriodilator

- increases coronary and cerebral blood flow

- minimal myocardial depression but may induce reflex tachycardia

- IV administration results in fall in BP in 5-15 min

- loading infusion of 10-15 mg/h until target reached and then maintenance of 2-5 mg/h
- adverse effects include headache, nausea and vomiting

Nimodipine

Mechanism of action

- blocks intracellular influx of calcium that is thought to be a central to ischaemic neuronal damage
- moderate cerebral vasodilator but does not reduce the incidence of angiographic spasm after Subarachnoid haemorrhage.

Pharmacokinetics

Absorption: rapidly absorbed from GI tract with peak plasma levels within 1 hour. Levels similar to those achieved during intravenous infusion

Adverse reactions

- uncommon

- small reduction in BP usual but may be severe in some patients treated with IV nimodipine.
- flushing

- LFT abnomalities and jaundice reported occasionally

- **Corticosteroids**

Mechanism of action

- enter cells where they combine with steroid receptors in cytoplasm
- combination enters nucleus where it controls synthesis of protein, including enzymes that regulate vital cell activities over a wide range of metabolic functions including all aspects of inflammation
- formation of a protein that inhibits the enzyme phospholipase A_2 which is needed to allow the supply of arachidonic acid. Latter is essential for the formation of inflammatory mediators
- also act on cell membranes to alter ion permeability
- also modify the production of neurohormones

Actions

Important to distinguish between physiological effects (replacement therapy) and pharmacological effects (occur at higher doses)

a. Mineralocorticoid

- Na retention by renal tubule
- increased K excretion in urine

b. Glucocorticoid

- CHO metabolism: increased gluconeogenesis, ± peripheral glucose uptake may be decreased with resultant hyperglycaemia ± glycosuria
- protein metabolism: anabolism is decreased but catabolism continues unabated or is increased resulting in negative N balance and muscle wasting.
- fat deposition: increased on shoulders, face and abdomen
- inflammatory response depressed
- allergic response depressed
- antibody production reduced by large doses
- lymphoid tissue reduced (including leukaemic lymphocytes)
- decreased eosinophils
- renal urate excretion increased
- euphoria or psychotic states may occur. ? due to CNS electrolyte changes
- anti-vitamin D action
- reduction of hypercalcaemia (chiefly where this is due to increased absorption from gut: vit D intoxication, sarcoidosis)
- increased urinary Ca excretion. Renal stones may form
- growth reduction where new cells are being added (eg in children) but not where they are replacing cells as in adult tissues
- suppression of HPA axis.
- Normal daily secretion of hydrocortisone is 10-30 mg. Exogenous daily dose that completely suppresses cortex is 40-80 mg (or prednisolone 10-20 mg).
- Prednisolone is standard choice for anti-inflammatory therapy. Can be given orally or IM

- Methylprednisolone used for IV pulsed therapy
- dexamethasone longer acting.
- fludrocortisone used to replace aldosterone where the adrenal cortex has been destroyed
- beclomethasone and budesonide used by inhalation for asthma. About 90% of inhalation dose is swallowed and inactivated by first-pass hepatic metabolism (steroids listed above are protected from this by protein binding). The rest, which is absorbed from the mouth and lungs gives very low systemic plasma concentrations. Although risk of HPA axis suppression is very low it can happen.

Pharmacokinetics

Administration: PO/IM/IV/intra-articular/topical/inhaled. Absorption after oral administration is rapid. Maximum biological effect seen after 2-8 h

Distribution: high plasma protein binding (95% in case of hydrocortisone) to transcortin and when this is saturated to albumin (80% in the case of hydrocortisone).

Adverse effects

In general serious unwanted effects are unlikely if daily dose is < 50 mg hydrocortisone or 10mg of prednisolone or equivalent

- Iatrogenic Cushings
- Avascular necrosis of bone
- Depression and psychosis
- Peptic ulceration
- Others include cataract (chronic use), glaucoma (prolonged use of eye drops), raised ICP and convulsions, blood hypercoagulability, menstrual disorders, fever
- Immunosuppression
- HPA axis suppression: dependent on steroid used, dose, duration of administration and time of administration. Single morning dose of <20mg prednisolone does notusually cause suppression while 5mg in evening suppresses early morning activation of HPA axis

Treatment of intercurrent illness

- maximum stress-induced output of cortisol is 200-300 mg/day
- production following surgery tends to be much less. Based on normal cortisol production rates the recommended daily doses of hydrocortisone equivalent for different categories of surgery are:

	Daily dose	Duration
Minor (eg hernia repair)	25 mg	1 day
Intermediate (eg cholecystectomy, colectomy, joint replacement)	50-75 mg	2 days
Major (eg oesophagectomy, cardiac surgery requiring CPB)	100-150 mg	2-3 days

- **Anti-convulsants**

Fosphenytoin

IV/IM administration

Clinical uses

- status epilepticus
- prophylaxis of seizures in patients with head injury or following neurosurgery
- patients unable to take enteral phenytoin

Adverse effects

Less common than with phenytoin. Many of the side effects of the latter are thought to be related to the carrier substance.

- severe cardiovascular adverse effects have been reported in patients receiving IV preparation
    - asystole, VF
    - hypotension
    - bradycardia
    - heart block
- majority of side effects occur within 30 minutes of infusion

Hydralazine

Pharmacokinetics

Admin: PO/IV. Approx 20% bioavailability when given orally, probably due to first-pass hepatic metabolism

Pharmacodynamics

- Direct arteriodilator with little venodilator action

- Reduces diastolic pressure more than systolic

- May induce reflex tachycardia and increased cardiac output which may blunt its hypotensive effect. Combination with a central alpha-2 agonist or a beta blocker decreases this reflex sympathetic activity

- improves renal and uteroplacental blood flow in pre-eclampsia

- onset time 10-20 min. Duration of action 6-8 h

Adverse effects

- reflex tachycardia

- headaches,

- nausea & vomiting

- flushing

- skin rash

- lupus syndrome: more likely to develop after prolonged therapy, in slow acetylators and in patients with renal failure

- infusions may be difficult to titrate in pre-eclampsia and may be associated with a higher incidence of fetal distress

- in presence of hypovolaemia may result in hypotension and fetal distress
- neonatal thrombocytopenia (rare)

Dose

- in hypertensive emergencies: IV boluses of 10-20 mg, repeated as necessary at 15 min intervals, to a maximum of 50 mg. Can also be given as an infusion: 0.5-1 mg/min
- in pre-ecplamsia for control of BP: 5 mg IV initially followed by 5-10 mg every 20 min to maximum of 40 mg

- **Cyclosporin**

Mode of action

- inhibits activation of T-cells without causing myelosuppression
- exact site of action is not well defined

Pharmacokinetics

Administration*:* IV/PO. Bioavailability 20-50%. Peak concentrations 3-4 h after dosing

Adverse effects

- Nephrotoxicity. 3 clinical syndromes:

  - *acute toxicity*: occurs in first 7 days of treatment. Usually presents as oliguria in patients who have received a cadaveric renal transplant but may also occur in native kidneys in patients who are treated with high doses.

  - *subacute*: generally occurs after at least 7 days of treatment and is present in varying degrees in all patients treated with cyclosporin. Both acute and subacute forms appear to mediated by a reversible increase in renovascular resistance.

  - *chronic*

- hypertension

- **Intensive insulin therapy**

- Tight control of blood sugar in the range of 4.4-6.1 mmol/l associated with improved outcome. There is evidence to suggest that the beneficial effect results from non-glucose related effects of insulin:
  - anti-inflammatory effect
  - prevention of immune paralysis

Ischaemic heart disease

- some evidence to suggest that glucose-insulin-potassium (GIK) infusions may improve outcome following acute myocardial infarction and following coronary artery bypass surgery.

2.13 Immunoglobulin

Preparation

- batched blood product prepared from 1,00-15,000 plasmapheresis and blood donations
- >95% IgG with trace amounts of IgM and IgA

Clinical uses

a. Immunomodulatory therapy

- **Neuromuscular disorders**

Established therapy for:

- Guillain-Barre
- Multifocal motor neuropathy with conduction block
- Chronic inflammatory demyelinating polyneuropathy
- myasthenia gravis unresponsive to other therapies
- Eaton-Lambert syndrome
- inflammatory myopathies:
    - polymyositis
    - dermatomyositis
    - inclusion body myositis

- **Dermatological disorders**

- Kawasaki disease. Reduces incidence of coronary aneurysms if given within 10 days of symptom onset
- Blistering disorders (eg pemphigus, pemphigoid) frequently treated with IVIG although controlled data supporting efficacy is limited
- Toxic epidermal necrolysis.

- **Vasculitic disorders**

- ANCA associated systemic vasculitis

- **Infection**

- Streptococcal toxic shock syndrome

- **Haematological**

- ITP
- Haemophagocytic syndrome
- Autoimmune haemolytic anaemia

- **Immunoreplacement**

- Acquired hypogammaglobulinaemia secondary to haematological malignancies (chronic lymphocytic leukaemia, multiple myeloma, non-Hodgkins lymphoma etc)
- primary immunodeficiency diseases with antibody deficiency

Contraindications

- Antiphospholipid syndrome (non-obstetric)
- Haemolytic uraemic syndrome
- Sepsis
- others

Adverse effects

- Headaches, backache, chills, nausea, myalgia
  - usually infusion rate-related
  - more common in patients with co-existing infection
- Anaphylaxis (very rare)

Metoclopramide

Mode of action

- lowers pressure threshold for occurrence of intestinal peristaltic reflex
- reduces intestinal muscle fatigue

- enhances frequency and amplitude of longitudinal muscle contraction
- coordinates gastric, pyloric and duodenal activity to improve GI motility
- mechanism of action appears to depend on intramural cholinergic neurons. Appears that acts primarily by augmenting release of ACh and perhaps by inhibition of 5-HT release
- increases lower oesophageal sphincter pressure

- **N-acetylcysteine**

Indications

Major indication: paracetamol poisoning

- patients with paracetamol level above or just below treatment line

- all patients with potentially hepatotoxic overdose (> 150 mg/kg). Treatment can be stopped if paracetamol concentration is below standard treatment line but this approach avoids potentially fatal delays in treatment
- all patients with evidence of severe toxicity or fulminant hepatic failure, regardless of time since overdose
- high risk patients (eg chronic alcohol abusers, malnutrition, HIV infection) with depleted hepatic glutathione, patients on enzyme inducing drugs (eg rifampicin, anticonvulsants, alcohol): start treatment at paracetamol levels half those of the standard treatment line
- patients unable to give a reliable history or who have taken a sequential overdose over several hours

Other indications

- toxicology: to prevent hepatotoxicity due to $CHCl_3$ or CCl_4 or neuropsychiatric sequelae of CO poisoning
- cardiology: to reduce tolerance to prolonged GTN infusion; in severe unstable angina and acute MI
- acute lung injury
- acute hepatic failure
- oncology: to prevent cardiotoxicity of doxorubicin and reduce haemorrhagic cystitis due cyclophosphamide and ifosfamide

Complications

At usual doses

- local skin reactions
- anaphylactoid
- hypertension

Overdose

- severe anaphylactoid reactions
- respiratory depression
- haemolysis
- DIC
- renal failure
- ARDS
- GI haemorrhage
- death

- **Recombinant human B-type (brain) natriuretic peptide**

Mode of action

- Vasodilatory, natriuretic and diuretic effects

- Primarily mediated via natriuretic peptide receptor A on vascular smooth muscle, endothelium, kidneys and adrenals
- No direct inotropic effect
- Reduces aldosterone and inhibits plasma renin activity

Pharmacokinetics

- administration: IV infusion
- distribution
    - mean volume of distribution at steady state 0.19 l/kg
- elimination by multiple routes:
    - after binding to cell surface natriuretic peptide receptor C nesiritide is internalized and degraded
    - hydrolysis by endopeptidase
    - renal filtration
- clearance proportional to body weight
- dosage adjustment not required in patients with renal dysfunction

Clinical indications

- Acute decompensated heart failure with dyspnoea on minimal exertion or at rest
    - reduces preload. Rapid reduction in pulmonary capillary wedge pressure (faster than glyceryl trinitrate) and right atrial pressure
    - reduces afterload resulting in increase in cardiac output
    - diuresis & natriuresis
    - 6 month mortality similar to patients treated with nitrate but lower than those treated with dobutamine
- contraindicated in cardiogenic shock or in patients with systolic BP <90 mmHg

Adverse effects

Cardiovascular

Similar incidence to patients treated with nitrate.

- hypotension
    - usually resolves spontaneously or responds to fluid challenge of 250 ml or less
    - duration of episode longer than hypotensive episodes associated with glyceryl trinitrate
- not proarrhythmic

Non-cardiovascular

Less common than with glyceryl trinitrate

- general pain
- abdominal pain

- catheter-related pain
- headache
- nausea

Drug interactions

- does not interact with enalapril
- interactions with IV vasodilators (including IV ACE inhibitors) and other cardiovascular drugs have not been formally studied

Dosage & administration

- bolus of 2 mcg/kg followed by infusion of 0.01 mcg/kg/min
- reduce dose/discontinue if hypotension occurs
- should only be used in pregancy if potential benefit to mother outweighs potential risk to fetus
- administer with caution to breastfeeding mothers

➢ Proton pump inhibitors

Pantoprazole

Pharmacokinetics

- adminstration: oral or IV infusion
  - bioavailability ~77%
  - absorption unaffected by food or antacids
- elimination: completely metabolized by cytochrome P450 with metabolites excreted predominantly in urine
- dosage adjustment not required in elderly and in patients with renal failure
- no clinically significant drug interactions

Adverse effects

- uncommon (<0.2% of patients)
- diarrhoea, nausea, vomiting, flatulence
- headache, vertigo
- exanthema, urticaria

➢ Benzodiazepines

Types

- 1:4 benzodiazepines eg chlordiazepoxide, midazolam
- 1:5 eg clobazam

Pharmacology

- benzodiazepine receptors associated with GABA chloride channel complex ($GABA_A$ receptor). GABA agonists cause opening of the Cl channel.

Diazepam

Administration

- PO/IV/IM
  - more reliably absorbed following oral than IM admin: may be due to precipitation in the muscle
  - IM injection of diazemuls very painful
  - peak plasma levels 1 hr after oral admin
  - In social concentrations (10%) alcohol slows absorption.
  - Oral abs of all orally administered benzodiazepines increased by concurrent metoclopramide; speeds gastric transit; and decreased by factors that decrease gastric emptying eg presence of food, aluminium antacids, opioids. Increase in gastric pH (eg following administration of H2 blockers) decreases ionization and therefore speeds absorption but overall aluminium antacids decrease rather than increase speed of absorption.

➢ **Midazolam**

Administration

- only available in injectable form.

Distribution and elimination

- shorter duration of action than diazepam because of rapid re-distribution
- imidazole ring opens up - changes from water to lipid soluble at pH > 4
- metabolism inhibited by inhibitors of cytochrome P450 system (eg propofol, diltiazem, erythromycin)

Endocrine

- midazolam infusion blunts ACTH response to surgery
- very high concentrations of midazolam and diazepam and their metabolites suppress bovine adrenal cortisol synthesis in vitro

ICU sedation

1.Midazolam

- satisfactory hypnotic in patients who are also receiving analgesia
- in patients with multiorgan dysfunction unpredictable half-life may be a problem

- may impair verbal contact and cooperation, particularly during weaning, because of potent amnesic properties. Attempts to control agitated patients with larger doses results in over-sedation
- protective effect against cerebral ischaemic damage

2.Diazepam & lorazepam

- can be given as intermittent boluses
- enteral lorazepam may be particularly useful in patients in patients requiring prolonged sedation

3.Flumazenil

Pharmacokinetics

- admin: IV/PO but 84% first-pass metabolism. IM injection may be painful
- after IV dose, distributed throughout the body within 5 mins. Maximal brain levels 5-8 mins after injection
- 99.8% metabolized in the liver
- $t_{1/2}$ 0.7-1.3 hrs
- plasma protein binding approx 40%

Clinical use

- reversal of benzodiazepine sedation. NB may wear off before benzodiazepine agonist
- specific reversal of the central effects of benzodiazepines in patients in ITU to allow return of spontaneous respiration and consciousness

Contraindications

- patients known to be hypersensitive to benzodiazepines
- epileptic patients after prolonged administration of benzodiazepines
- reversal of anaesthesia in the presence of neuromuscular blockade

Dosage

- reversal of midazolam sedation: 0.005-0.01 mg/kg. Titrate in increments of 0.1-0.2 mg. Resedation is possible but unlikely in this situation if the flumazenil is given as the midazolam effect is waning
- if used to antagonize effect of OD, or after prolonged use or use of a longer-acting drug, infusion may be more appropriate: 100-400 mcg/hr

Preparation

- 1% emulsion of soyabean oil, glycerol and egg phosphatide
- provides 1.1 kcal/ml

Pharmacokinetics

- IV administration
- hepatic and extra-hepatic metabolism. Latter results in relatively short duration of action even in patients with hepatic failure

Mode of action

Not clear but appears to involve GABA receptors in CNS

Clinical use

- recommended for short term (<24h) sedation in ICU
- propofol bottles, syringes and infusion tubing should be changed every 12 hours because of risk of infection

Adverse effects

- myocardial depression and vasodilation leading to hypotension
- hypertriglyceridaemia and pancreatitis
- pain on injection
- rarely metabolic acidosis, rhabdomyolysis and cardiovascular collapse

4.Theophylline

a) Xanthine

Mode of action

- relaxes bronchial smooth muscle but mode of action not completely understood
- probably involves competitive inhibition of adenosine receptors
- inhibition of phosphodiesterase is negligible at therapeutic concentrations
- improves diaphragmatic contraction
- increases rate and force of cardiac contraction
- increases rate of urine production

Pharmacokinetics

Administration: PO: absorption usually rapid and complete. Theophylline is relatively insoluble. Aminophylline is a mixture of theophylline with ethylenediamine which is sufficiently soluble for IV use. Give by slow IV injection/infusion

Clinical uses

- Chronic and acute asthma

- COPD

Adverse effects

- nausea and diarrhoea at high therapeutic levels
- cardiac arrhythmias and fits when plasma concentration exceeds recommended range

Drug interactions

- Reduced rates of theophylline elimination due to enzyme inhibition by: erythromycin, ciprofloxacin, allopurinol, oral contraceptives
- Enhanced elimination due to enzyme induction by: carbamazepine, phenobarbitone, phenytoin

5. Ionotropes and vasopressors

Alpha receptors

- post synaptic cardiac alpha$_1$ receptors:
- - stimulation causes significant increase in contractility without an increase in rate
  - not mediated by cAMP

  - effect more pronounced at low heart rates

  - slower onset and longer duration than beta$_1$ receptor mediated response

- presynaptic alpha$_2$ receptors in heart and vasculature appear to be activated by norepinephrine released by sympathetic nerve itself and mediate negative feedback inhibition of further norepinephrine release
- post synaptic alpha$_1$ and alpha$_2$ receptors in peripheral vessels mediate vasoconstriction

- Beta receptors

- post synaptic beta$_1$ receptors are predominant adrenergic receptors in heart. Stimulation causes increased rate and force of cardiac contraction. Mediated by cAMP
- post synaptic beta$_2$ receptors in vasculature mediate vasodilatation

-Dopamine receptors

- peripheral DA$_1$ receptors mediate renal, coronary and mesenteric arterial vasodilatation and a natriuretic response
- DA$_2$ receptors: presynaptic receptors found on nerve endings, inhibit norepinephrine release from sympathetic nerve endings, inhibit prolactin release and may reduce vomiting
- stimulation of either DA$_1$ or DA$_2$ receptors suppresses peristalsis and may precipitate ileus

6.Dopamine

Immediate precursor of norepinephrine and epinephrine

Pharmacodynamics

Dose dependent effects:

- <5 m g/kg/min predominantly stimulates DA_1 and DA_2 receptors in renal, mesenteric and coronary beds. Þ vasodilatation
- 5-10 m g/kg/min: b $_2$ effects predominate. Þ cardiac contractility and HR
- >10 m g/kg/min: a effects predominate Þ arterial vasoconstriction and BP

Pharmacokinetics

Marked variability in clearance in the critically ill. As a result plasma concentrations cannot be predicted from infusion rates

Clinical use

- variable effects due to variable clearance
- increases cardiac output (mainly due to increased stroke volume) with minimal effect on SVR in patients with septic shock
- increases pulmonary shunt fraction
- effects on splanchnic perfusion unclear
- increases urine output without increasing creatinine clearance in a number of settings.
- Low dose dopamine does not prevent renal failure in critically ill patients

7. Dobutamine

Possesses the same basic structure as dopamine but has a bulky ring substitution on the terminal amino group-Synthetic catecholamine

Pharmacodynamics

- strong +ve inotropy due to $beta_1$ agonist effects and $alpha_1$ agonism

- mild +ve chronotropy due (+) isomer effect on beta receptors

- weaker alpha receptor blockade and $beta_2$ stimulation, produced by (+) isomer and $alpha_1$ agonism produced by(-) isomer

Pharmacokinetics

Administration: slow IV.

8. Epinephrine

Pharmacokinetics

Admin: IV/IM/infiltration

Pharmacodynamics

- stimulates alpha$_1$ and both beta$_1$ and beta$_2$ receptors. Effects are mediated by stimulation of adenyl cyclase resulting in an increase in cAMP

- beta2 receptors more sensitive to epinephrine than alpha1

CVS

- positive inotrope and chronotrope (NB. mediated by all 3 receptors not just beta$_1$)
- increases incidence of dysrhythmias by increasing irritability of automatic conducting system
- constricts vessels of skin, mucosae, subcutaneous tissues, splanchnic area, kidneys (alpha effects)
- vessels of muscle and liver are dilated at physiological doses (beta effect) but are constricted at higher doses.

- cerebral and pulmonary arteries are constricted

Renal

- RBF and urine output reduced

RS

- bronchial tone decreased

- depth of respiration slightly increased

- irregular breathing sometimes seen

- decreases mucosal blood flow; results in reduced mucosal oedema and bronchial secretions

GI tract

- muscle of gut relaxed, pyloric and ileocolic sphincters constricted: leads to ileus
- intestinal secretion inhibited

- spleen contracts and empties its cells into the circulation

Metabolic

- beta stimulation causes increased insulin and glucagon secretion, alpha decreased. Overall epinephrine has anti-insulin effect.

- increased blood glucose due to increased mobilization of glycogen.

- rise in metabolic rate.

- plasma K rises initially due to increased release from liver.

- net result is an increase in O_2 consumption

- may result in lactic acidosis

CNS

- CNS stimulation usually very modest

- pupillary dilatation

- elevates pain threshold

- at high doses:anxiety, restlessness from mild cerebral stimulation, throbbing headache, vertigo

Clinical use

- Infusion rates of 0.04-1 m g/kg/min required to increase haemodynamic and oxygen transport variables to supranormal values in septic patients
- In septic patients Þ MAP predominantly by SV with more modest HR and SVR. Dose response for SVR unpredictable.¯ splanchnic blood flow and serum lactate.
- Minimal effect on PA pressures

Contraindications

- patients on MAOIs, tricyclics or receiving halothane, because of risk of VF
- hypertension

- hyperthyroidism

9. Norepinephrine

- alpha and $beta_1$ agonist with no clinically significant $beta_2$ effects
- equipotent with epinephrine as a $beta_1$ agonist but less potent an alpha agonist in most

tissues
- used for refractory hypotension

- may result in no change or slight decrease in cardiac output and oxygen delivery due to increased afterload

Clinical use

- in doses of 0.01-2 m g/kg/min reliably and predictably improves haemodynamic variables to normal or supranormal values in the majority of septic patients
- effect on oxygen transport variables cannot be determined from current data

Ephedrine

Naturally occurring amine with both direct and indirect (stimulates norepinephrine release from postganglionic sympathetic nerve endings) sympathomimetic effects.

Pharmacodynamics

- both alpha and beta agonist effects

- haemodynamic effects are similar to epinephrine but it has a longer duration of action and is active when administered orally

- increased cardiac contractility and heart rate and thus cardiac output
- may increase cardiac irritability

- relaxes bronchial and other smooth muscle, but less effective than epinephrine
- reduces uterine muscle activity

Pharmacokinetics

Administration: PO/IV

10. Methoxamine

Pharmacodynamics

- direct and indirect effects

- alpha agonist and beta blocker

- primary effect is peripheral vasoconstriction resulting in rise in systolic and diastolic BP
- HR slows due to beta blocking effects and reflex slowing due to rise in BP

- no effect on cardiac contractility and so cardiac output falls

Indications and dosage

- hypotensive states due to excessive vasodilatation eg spinal or epidural block
- 5-10 mg IV acts within 2 mins. Effect persists for about 20 mins. Dose can be titrated against effect in 2 mg boluses

Contra-indications

- patients on MAOIs

- history of hypertension

Toxicity

- excessive rise in BP; may precipitate myocardial ischaemia

- vomiting, headache, desire to micturate, significant reduction in HR

- treat with IV alpha blocker (eg phentolamine)

11. Phenylephrine

- similar effects to norepinephrine but probably even shorter acting

- direct acting

- potent alpha and weak beta agonist

- causes peripheral vasoconstriction and thus a rise in BP, especially diastolic

- often reflex reduction in heart rate

- only direct effect on heart is to slightly increase myocardial irritability

- largely replaced by catecholamines

12. Phosphodiesterase inhibitors

-Inhibit phosphodiesterase in cardiac tissue thereby increasing the level of intracellular cAMP (phosphodiesterase inactivates cAMP) and increasing intracellular calcium availability by causing increased calcium influx via slow channel. This increases rate and force of myocardial contraction

- cAMP also affects diastolic heart function through the regulation of phospholamban (regulatory subunit of the Ca pump of the sarcoplasmic reticulum. Enhances Ca re-sequestration rate and hence improves diastolic relaxation

- synergistic with beta agonists

- also relax vascular smooth muscle resulting in vasodilatation.

- myocardial oxygen consumption and heart rate are not significantly increased

- tolerance is not a feature

- Inhibit platelet aggregation

- Reduce post-ischaemic reperfusion injury

13. Enoximone

Pharmacology

- belongs to imidazoline class of cardioactive drugs

- metabolised to an active metabolite which is excreted in the urine.
- elim half life is about 2 hours in normal subjects but about 7 hours in patients with cardiac failure (half life of dobutamine is 2-3 minutes)

Clinical studies

- vasodilator, weak inotrope and even weaker chronotrope.

- increases cardiac index and reduces ventricular filling pressure by about 50% in patients with CCF.

- inotropic effect may be potentiated by catecholamine such as dobutamine.
- no evidence that it increases long term survival in patients with CCF.

Adverse effects

- abnormal LFTs

- thrombocytopaenia

Dose

Loading: 0.5-1 mg/kg

Maintenance: 5-10 mcg/kg/min

3. Conclusion

The drug delivery rate is an important factor when administering IV medication. Some IV drugs are meant to be delivered rapidly over several minutes to obtain therapeutic effect. Other drugs are most effective when delivered slowly and intermittently throughout the day. Each drug delivery rate is unique. Administration guidelines for giving IV medications must be followed to achieve the therapeutic effect desired.The health care professional must know the indications, actions, and adverse effects of the medication that is to be delivered and must observe the patient closely for adverse medication reactions or allergic reactions and be prepared to respond with supportive therapy or drug reversing agents.

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