

Pharmacology Handout – Level Two

DRUGS RELATED TO THE CARDIOVASCULAR SYSTEM

GLYCOSIDES

Digoxin – increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node. Useful in the treatment of supraventricular tachycardias such as atrial fibrillation and cardiac failure. Ventricular rate should not fall below 60 per minute when on maintenance. May be given IV, not IM. 125-250 micrograms twice a day for a week to establish satisfactory plasma levels and then reduce dosage. Long half-life therefore maintenance dose daily and reduced – 62.5 to 500 micrograms daily. Digoxin toxicity at plasma levels 1.5-3 micrograms per litre, elderly susceptible, hypokalaemia susceptible. Signs of toxicity – anorexia, N&V, abdominal pain, visual disturbance, headache, fatigue, drowsiness, confusion, delirium, hallucinations, depression, arrhythmias, heart block, gynaecomastia, thrombocytopenia. Urgent treatment of toxicity (available poisons centres) – digoxin-specific antibody fragments. Beware of pre-existing heart blocks, recent MI, renal impairment.

KEY POINTS – DIGOXIN

1. Starting dose in mild heart failure 125-250 micrograms BD
2. Maintenance dose often once daily
3. Rapid digitalisation in severe heart failure 0.75-1mg by IV infusion over 2 hours
4. IM injection painful, not recommended
5. Nausea, vomiting and visual disturbances indicate reduction of dose
6. Specific antidote is digoxin specific antibody
7. Do not give digoxin if pulse rate below 60

PHOSPHODIESTERASE INHIBITORS

Enoximone – selective phosphodiesterase inhibitor exerting effect on myocardium. CCF where cardiac output is reduced and filling pressures are increased. Beware if HOCM or any obstructive component to valves. Can cause ectopics, hypotension, headache, insomnia, N&V, diarrhoea, chills, fever. 0.5 to 1mg per kg initially IV (slow) then 500 micrograms per kg every 30 minutes up to a maximum of 3mg/kg. Infusion 90 micrograms/kg/min over 10-30 mins. Repeat every 3-6 hours as necessary.

DIURETICS

Thiazides – moderately potent diuretics acting by inhibiting sodium reabsorption at the beginning of the distal convoluted tubule. Work within 1-2 hours of oral intake and last for 12-24 hours. Lower doses efficient for lowering blood pressure, increasing dose causes changes in plasma potassium, uric acid, glucose and lipids.

Bendrofluazide – use in oedema and hypertension. May cause hypokalaemia, aggravate gout and diabetes, exacerbate SLE. Can cause postural hypotension, impotence, lower levels of potassium, sodium, magnesium and higher calcium, glucose and uric acid. For oedema 5-10mg daily, hypertension 2.5mg daily.

Indapamide – similar profile to thiazides. Used in essential hypertension. 2.5mg oral in the morning.

Metolazone – similar profile to thiazides. To treat oedema 5-10mg in the morning increasing to 20mg. Maxm dose 80mg daily.

Loop Diuretics – treatment pulmonary oedema, LVF. Reduces preload, can be used in hypertension. Used in conjunction with thiazides. Inhibit reabsorption from ascending of limb of loop of Henle. Hypokalaemia may develop. Beware enlarged prostate. Act within one hour orally and complete in six hours. Peak IV in 30 minutes. Both drugs can cause deafness.

Frusemide – do not exceed 4mg/min IV. Beware liver and renal failure. Side effects – hyponatraemia, hypokalaemia, hypomagnesaemia, hyperuricaemia, hyperglycaemia, increased calcium excretion, tinnitus and deafness. 20-40mg daily, oliguria 250mg daily.

Bumetamide – same side effects plus myalgia. 1mg repeated after 6-8 hours, up to 5mg per day.

Potassium Sparing – weak diuretics, retention of potassium.

Amiloride – use in conjunction with loop or thiazide. Contraindicated in hyperkalaemia, renal failure. Can cause GIT disturbance, dry mouth, confusion, postural hypotension. 10mg daily or 5mg BD, maxm 20mg daily.

Aldosterone Antag – potassium sparing and potentiates both loop and thiazide diuretics. Useful in oedema caused by liver failure and Conn's syndrome.

Spironolactone – use in cirrhosis, nephrotic syndrome. Beware hyperkalaemia. Do not use if hyponatraemia. Can cause GIT disturbance, impotence, gynaecomastia, irregular periods, lethargy, headache. 100-200mg daily.

KEY POINTS – DIURETICS

1. Thiazides are used mainly to reduce oedema due to heart failure and in hypertension
2. Loop diuretics are of value in pulmonary oedema caused by LVF and when response to thiazides is inadequate
3. Hypokalaemia is potentially dangerous in patients with coronary artery disease receiving digoxin or anti-arrhythmic drugs
4. Best taken in the morning to reduce nocturia
5. May cause postural hypotension especially after sleep
6. Note any sign of electrolyte disturbances such as tachyarrhythmias, muscle weakness (hypokalaemia), lethargy (hyponatria), tingling and numbness (hypocalcaemia), bone pain nausea and confusion (hypercalcaemia)

ANTI-ARRHYTHMICS

Types of arrhythmias :-

Ectopic beats – spontaneous with a normal heart, no problem. Can treat with beta blockers.

Atrial fibrillation- ventricular rate at rest can be treated with digoxin, if still high at rest or exercise, add beta blocker or verapamil. Anticoagulants if elderly, valvular or myocardial disease.

Atrial flutter - ventricular rate at rest can be treated with digoxin. DC shock can be used. Amiodarone can be used to restore sinus rhythm and maintain it (or sotalol). Anticoagulant before DC shock.

Paroxysmal supraventricular tachycardia – can be treated with reflex vagal stimulation, carotid sinus massage or Valsalva. IV adenosine or verapamil (no myocardial or valvular disease). Never use if patient on beta blockers. DC shock. Beware digoxin toxicity.

Arrhythmias after MI – always ensure ECG record available. Atropine for bradycardia.

Ventricular tachycardia – lignocaine drug of first instance. DC shock.

Treatment :-

Classified according to effect on electrical behaviour of myocardial cells during activity (Vaughan Williams classification). Negative inotropic effect of antiarrhythmic drugs is additive and hypokalaemia potentiates arrhythmic problem.

- Class 1 – (sodium channel blockers) disopyramide, flecainide, lignocaine, mexilitene, procainamide, propafenone, quinidine, tocainide
- Class 2 – (beta blockers) esmolol, metoprolol, pindolol, propanolol, sotalol
- Class 3 – (potassium channel blockers) amiodarone, bretylium, sotalol
- Class 4 – (calcium channel blockers) verapamil, diltiazem

- Others – adenosine, digoxin

Supraventricular arrhythmias – adenosine treatment of choice in parox. SVT – very short duration of action – half life 8 to 10 seconds, prolonged when taking dipyridamole. Can be used after a beta blocker. Verapamil preferable in asthmatics. Oral digoxin for slowing ventricular response in AFib and Flut. Avoid in SV arrhythmias assoc with Wolf-Parkinson-White syndrome. Verapamil for SVT, IV followed by oral – interacts with beta blockers, beware. Contraindicated in AF with pre-excitation (WPW). Beta blockers such as esmolol and propranolol for rapid control of ventricular rate.

Adenosine – treatment of SVT inc WPW. Contraindicated in 2nd or 3rd degree heart block, sick sinus syndrome and asthma. Flushing, dyspnoea, bronchospasm, nausea, bradycardia, lightheadedness. 3mg IV over 2 seconds. 6mg after 1-2 mins, then 12mg after further 1-2 mins.

Supraventricular and ventricular arrhythmias – amiodarone when other drugs are ineffective or contraindicated. Only initiate in hospital. Little cardiac depression. Long half-life extending to weeks, give daily. Contains iodine which may affect the thyroid. Disopyramide used after MI but impairs cardiac contractility. Also anti-muscarinic effects – beware glaucoma, prostate. Flecainide for serious ventricular arrhythmias and junctional re-entry tachycardias. Can precipitate serious arrhythmias.

Amiodarone – monitor liver and thyroid function and chest X ray before treatment. Do not use in severe conduction disturbances, iodine sensitivity, thyroid dysfunction and severe hypotension (IV). Causes corneal microdeposits, optic neuritis, peripheral neuropathy, phototoxicity, diffuse pulmonary alveolitis, pneumonitis, jaundice, N&V, tremor, flushes, sweats, nightmares, headache, sleeplessness, impotence, haematological changes, ataxia and rashes. 200mg TDS for 7 days, 200mg BD for 7 days followed by maintenance of 200mg daily. IV 5mg/kg over 20-120 mins (ECG monitoring) maxm 1200mg 24 hrs.

Disopyramide – ventricular arrhythmias after MI. Avoid in hypotension, partial block, bundle branch block, prostate/glaucoma, liver and renal impairment. Contraindicated in 2nd and 3rd degree block, sinus node dysfunction, cardiogenic shock and failure. Can cause VT and VF, myocardial depression, hypotension, AV block, jaundice and hypoglycaemia. 300-800mg per day; 2mg/kg IV over 5 mins to maxm 150mg followed by 200mg orally TDS.

Flecainide - arrhythmias associated with WPW, parox AF, sustained VT and premature ventricular contractions. Beware patients with pacemakers, 2nd degree+ block, bundle branch block, elderly. Contraindicated in CCF, history of MI, long standing AF, significant valvular heart disease. Dizziness, visual disturbance, urticaria, N&V, confusion, depression, convulsions, jaundice, similar to disopyramide. 50-100mg BD to maxm 300mg daily, IV 2mg/kg over 10-30 mins (ECG).

Ventricular arrhythmias – bretylium in resuscitation, IM or IV. Can cause severe hypotension (IV) and N&V. Lignocaine relatively safe by slow IV injection. Beware cardiac or hepatic failure. Mexiletine slow IV if lignocaine ineffective. N&V.

Mexiletene - ventricular arrhythmias after MI. Beware hepatic impairment. Contraindicated in bradycardia, cardiogenic shock, AV block. Can cause N&V, constipation, bradycardia, hypotension, AF, palpitations, drowsiness, convulsions, ataxia, tremor, jaundice. Oral 400mg followed by 200-250mg TDS or QDS. IV 100-250mg at rate of 25mg/min (ECG) then infusion 250mg over 1 hr, 125mg/hr for 2 hrs then 500mcg/min.

Lignocaine – ventricular arrhythmias after MI. Beware elderly, cardiac and hepatic failure. Contraindicated in AV block and severe myocardial depression. Can cause dizziness, paraesthesia or drowsiness. Confusion, convulsion, hypotension and bradycardia. 100mg bolus IV over few mins followed by infusion of 4mg/min for 30 mins, 2mg/min for 2 hrs and 1mg/min thereafter.

KEY POINTS – ANTI-ARRHYTHMIC DRUGS

1. Determine type of arrhythmia by ECG before treatment
2. Adenosine in paroxysmal supraventricular tachycardia
3. Verapamil is used in supraventricular arrhythmias (not if recently treated with beta blockers)
4. Lignocaine and similar drugs in ventricular arrhythmias
5. Bretylium is used only in resuscitation

NICE RECOMMENDATIONS ATRIAL FIBRILLATION

If left untreated there is a significant risk of stroke and other morbidities. Confirm with ECG. Persistent AF – rate control (>65yrs, coronary heart disease, contraindications to drug therapy, no congestive failure) or rhythm control (symptomatic, younger patients, first time lone AF, congestive failure), appropriate anti-thrombotic therapy. Permanent AF – rate control with beta blockers or rate limiting calcium antagonists; digoxin in sedentary patients. If monotherapy inadequate add digoxin. Paroxysmal AF – avoid precipitant, standard beta blocker; no structural heart disease flecainide or propafenone; unsuccessful amiodarone. Plus coronary heart disease sotalol; plus poor left ventricular function amiodarone. Acute onset AF – CVS unstable then electrical cardioversion, if delay amiodarone; if WPW flecainide, rate control beta blocker, calcium antagonist or amiodarone. Heparin the initial anti-thrombotic then oral. Post-operative AF – (prophylaxis in cardiac surgery) amiodarone, beta blocker or sotalol. Electrical cardioversion – prolonged AF, onset more than 48 hrs previously. Pharmacological cardioversion – persistent AF use Class 1c drug (flecainide or propafenone) when no structural heart disease or amiodarone with structural heart disease. Amiodarone or sotalol for at least 4 weeks before electrical cardioversion. Anti-thrombotic therapy – before cardioversion at least 3 weeks with INR 2.5 (range 2-3), after successful cardioversion INR 2.5 for 4 weeks. Permanent AF – warfarin INR 2.5 or aspirin 75-300mg daily

BETA BLOCKERS

Block beta receptors in heart, peripheral vasculature, bronchi, pancreas and liver. Oxprenolol, pindolol and acebutolol have intrinsic sympathomimetic activity, causing less bradycardia and cold extremities. Water soluble less likely to cross into brain – atenolol and sotalol – less sleep disturbance and nightmares. Also excreted by kidneys – beware renal problems. Short duration of action. Daily for hypertension, BD for angina. Beta blockers can precipitate asthma. Atenolol, acebutolol and metoprolol less effect on B₂ receptors and are more cardioselective but not cardiospecific. Can be associated with fatigue and cold extremities, less common with ISA. May cause a slight deterioration in glucose tolerance in diabetics. In hypertension they reduce cardiac output, alter baroreceptor reflex sensitivity and block peripheral adrenoreceptors. Some depress plasma renin secretion and a central action has not been ruled out. Used in the control of pulse rate in pheochromocytoma (always use with concurrent alpha blockade). In angina cardiac work is reduced. Sudden withdrawal may precipitate attack. Beta blocker with verapamil may precipitate CCF. Can reduce the recurrent rate in MI. Atenolol and metoprolol can reduce early mortality after IV dose. In arrhythmias beta blockers attenuate the effect of the sympathetic nervous system. It controls the ventricular response in AF, SVT and thyrotoxicosis. Esmolol, short acting and cardioselective – useful in perioperative period. Used to relieve symptoms of anxiety and prophylaxis in migraine. Labetolol blocks beta₁ and alpha, alpha to beta activity is 1:2 orally and 1:7 IV. Bisoprolol has arteriolar vasodilating effect as well as beta blocking and carvedilol has less effect on beta₂ receptors and is relatively cardioselective.

Propranolol – beware abrupt withdrawal, first degree heart block, renal and liver disease. Contraindicated in asthma and COAD, bradycardia, hypotension, uncontrolled failure, heart block and severe peripheral vascular disease. All the above can present as side effects along with GIT disturbance, rash, sleep

problems. Hypertension 80mg BD orally, increasing weekly to a maintenance of 160-320mg per day. Angina 40mg BD or TDS increasing to 120-240mg daily. IV 1mg over one minute.

Atenolol - caution, contraindications and side effects same as propranolol. Hypertension 50mg daily, angina 100mg daily. IV 2.5mg at 1mg/min, five minute intervals to a maxm 10mg.

Labetolol - caution, contraindications and side effects same as propranolol. Plus postural hypotension. 100mg BD up to 200mg BD. IV 50mg over one minute (maxm 200mg).

Sotalol – life threatening arrhythmias, prophylaxis of parox atrial tachycardia or fibrillation. Caution, contraindications and side effects same as propranolol. Orally with ECG monitoring 80mg daily in divided doses, increasing at intervals of 2-3 days to 160-320mg daily (in divided doses). IV 20-120mg over 10 mins, 6 hour intervals.

Metoprolol - caution, contraindications and side effects same as propranolol. Hypertension 100mg daily, maintenance 100-200mg daily. Angina 50-100mg BD or TDS. IV 5mg at 1-2 mg/min repeated at 5 min intervals to a maxm of 10-15mg. .

Esmolol – short term treatment SV arrhythmias, tachycardia and hypertension during perioperative period. Caution, contraindications and side effects same as propranolol. IV infusion 50-200 mcg/kg/min.

Bisoprolol – same cautions and monitor for four hours after initiation in cardiac failure. Hypertension and angina 10mg daily (range 5-20mg daily). Heart failure 1.25mg daily for one week then increase to 2.5mg daily for one week if tolerated. 3.75mg daily for one week; 5mg daily for four weeks; 7.5mg daily for four weeks to a maximum of 10mg daily.

Carvedilol – same cautions. Side effects – postural hypotension, dizziness, headache, fatigue, GIT upset, diminished peripheral circulation, dry eyes, impotence. Hypertension 12.5mg daily increased after two days to 25mg daily then increase at intervals of two weeks to a maximum of 50mg daily. Angina 12.5mg BD increasing after two days to 25mg BD. Adjunct to heart failure 3.125mg BD increasing at intervals of two weeks to 6.25mg BD then to 12.5mg BD then to 25mg BD (maxm <85kgs; 50mg BD >85kgs).

KEY POINTS – BETA BLOCKERS

1. All have same basic action, but some (atenolol, sotalol, nadolol) are not lipid-soluble and are less likely to cause sleep disturbances
2. All cause bradycardia and could precipitate incipient heart failure
3. May bring about histamine release and cause bronchoconstriction
4. Patients should be warned about postural hypotension, particularly after sleep
5. Coldness in the extremities may occur as a result of reduced peripheral blood flow
6. Do not stop treatment abruptly and do not run out of supplies
7. No beta blocker should be given to a patient recently treated with verapamil

VASODILATORS

Hydralazine – orally useful adjunct to other treatment. Beware renal and liver impairment. May provoke angina. Contraindicated in SLE, severe tachycardia, heart failure. Can cause tachycardia, palpitations, LE like syndrome (long term treatment), peripheral neuritis, blood disorders. Hypertension 25mg BD, IV slow 5-10mg over 30 mins.

Sodium Nitroprusside – IV infusion to control severe hypertensive crises. Caution with ischaemic heart disease, thyroid and renal impairment. Contraindicated liver impairment, B₁₂ deficiency and Leber's optic atrophy. Side effects due to rapid decrease in BP. 0.5 to 1.5mcg/kg/min IV infusion (keep within a range of 0.5 to 8).

Minoxidil – used with beta blocker and diuretic. Sodium and water retention, weight gain, peripheral oedema, tachycardia, hypertrichosis, GIT upset. Dose initially 5mg (elderly 2.5mg) daily increased by 5-10mg every three or more days to a maxm of 50mg daily.

CENTRALLY ACTING ANTIHYPERTENSIVE DRUGS

Methyldopa can be used in hypertension associated with pregnancy. Moxonidine used in mild to moderate hypertension when other treatments have failed.

Methyldopa – caution in liver and renal impairment, depression, positive Coombs test in 20% patients. Side effects – GIT upset, dry mouth, stomatitis, bradycardia, headache, dizziness, myalgia, arthralgia, psychosis, depression. Dose 250mg BD to TDS increasing at intervals of two or more days to a maxm of 3gms daily.

Moxonidine – same cautions. Contraindication in history angioedema, conduction disorders, Parkinson's, glaucoma, pregnancy. Side effects – dry mouth, headache, fatigue, dizziness, nausea, sleep disturbance. Dose 200 micrograms once daily in the morning increasing after three weeks if necessary to 400 micrograms daily in divided doses (BD). Maxm 600 micrograms daily.

ALPHA BLOCKERS

Prazosin, doxazosin and indoramin have post-synaptic alpha blocking and vasodilator properties. Can cause rapid reduction of BP after first dose.

Doxazosin – used in hypertension and benign prostatic hypertrophy. Beware of liver impairment and susceptibility to heart failure. Can cause postural hypotension, dizziness, headache, fatigue, somnolence, rhinitis, D&V, rash and blood disorders. Hypertension 1mg daily increasing to 2mg after 1-2 weeks then 4mg (maxm 16mg daily).

Indoramin – beware alcohol, Parkinson's, heart failure, depression and epilepsy. Can cause extrapyramidal effects as well as those above. 25mg BD increased by 25-50mg daily at intervals of 2 weeks (maxm daily dose 200mg).

Prazosin – similar effects. Hypertension 500mcg 2-3 times daily, increasing to 1mg 2-3 times daily after 3-7 days (maxm 20mg daily). CCF 500mcg 2-4 times daily increasing to 4mg daily.

Phenoxybenzamine – powerful alpha blocker used in treatment of hypertension episodes associated with pheochromocytoma. Caution with elderly, congestive heart failure and renal impairment. Contraindicated with history of CVA and 3-4 weeks after MI. Can cause postural hypotension and GIT disturbances. 1mg/kg daily over 2hrs.

Phentolamine – short acting alpha blocker. Similar to phenoxybenzamine. 2-5mg IV.

KEY POINTS – ALPHA ADRENORECEPTOR BLOCKING AGENTS

1. Warn patients about hypotension, particularly first dose hypotension
2. Subsequent postural hypotension may be increased by hot baths, long standing and large meals
3. Advise patients to rest at any feeling or onset of faintness

RENIN ANGIOTENSIN (ACE)

Angiotensin converting enzyme inhibitors (ACE) inhibit the conversion of angiotensin I to angiotensin II. Used with a diuretic in heart failure, beware hyperkalaemia. Profound first dose hypotension can occur in heart failure patients on loop diuretics. Use in hypertension when thiazides and beta blockers are contraindicated, fail or are not tolerated. Useful in insulin dependent diabetics with hypertension. Should be initiated under clinical supervision. Can reduce or abolish glomerular filtration in patients with renal artery stenosis. Monitor renal function in all patients. Concomitant treatment with NSAID's can increase the risk. Can cause dry cough. Caution with patients on diuretics, peripheral vascular disease. Risk of agranulocytosis. Contraindicated in patients with a history of angioedema, renovascular disease and aortic stenosis. Can cause profound hypotension, rash, pancreatitis, rhinitis, GIT effects, N&V, abnormal LFT's, blood disorders.

Captopril – use in hypertension with thiazide diuretic, CCF and following MI. 12.5mg BD for hypertension to 50mg TDS in severe cases. Heart failure 25mg BD or TDS (maxm 150mg daily).

Enalapril – can cause palpitations, arrhythmias, angina and syncope. Stevens-Johnson syndrome, pulmonary infiltrates and alopecia. 5mg daily, 2.5mg if with diuretic (maxm 40mg daily).

Lisinopril – can cause CVA and MI, mood changes. Hypertension 2.5mg daily, to 10-20mg daily (maxm 40mg daily). Heart failure 2.5mg daily, maintaining at 5-20mg daily.

Perindopril – can cause sleep disturbance. Hypertension 2mg daily, then 4mg to a maxm 8mg.

Ramipril – can cause erythema multiforme and exacerbate Raynaud's. Hypertension 1.25mg daily and increase every 1-2 weeks to a maxm 10mg daily. MI prophylaxis 2.5-5mg BD.

KEY POINTS – ACE INHIBITORS

1. Check renal function and electrolytes before starting and during treatment
2. First dose hypotension may be marked
3. Reduce risk by withdrawing diuretic therapy for a few days and giving a low first dose at night with the patient in bed
4. Discontinue potassium sparing diuretics or potassium supplements to avoid risk of hyperkalaemia

ANGIOTENSIN II RECEPTOR ANTAGONIST

Specific angiotensin II receptor antagonists with properties similar to ACE inhibitors. Do not cause dry coughs – do not inhibit the breakdown of bradykinin and kinins. Same cautions as ACE inhibitors.

Losartan – diarrhoea, dizziness, myalgia, migraine, pruritis. 50mg daily, half dose in elderly and renal impairment. Increasing to 100mg once daily over a period of several weeks.

Valsartan – epistaxis, neutropenia, fatigue. 80mg once daily, half dose elderly and renal. Increasing to 160mg over several weeks.

Telmisartan – good oral bioavailability (50%). Avoid in active gastric or duodenal ulceration. GIT disturbance, pharyngitis, myalgia, backache. 40mg once daily increasing to a maximum of 80mg daily.

NITRATES

Vasodilator effect by arteriolar dilatation reducing both peripheral vascular resistance and left ventricular pressure at systole. Attacks of stable angina can be treated with sublingual GTN. Attacks more than twice a week require regular drug therapy. Unstable angina – caused by rupture of a plaque – admit to hospital. IV isosorbide or GTN for these patients. Coronary vasodilators exert their effect by reducing venous return, reducing left ventricular work. Can cause flushing, postural hypotension and headache. Sublingual GTN lasts for 20-30 minutes. Isosorbide is more stable, for infrequent users. Slower onset but can last for up to 12 hours. Tolerance is a problem with patches.

GTN – beware liver and renal impairment, hypothyroidism, recent MI. Contraindicated in hypotension, HOCM, pericarditis, anaemia, closed angle glaucoma and mitral stenosis. Can cause headache, flushing and postural hypotension. Sublingual 0.3-1mg repeated as required. IV infusion 10-200mcg/min.

Isosorbide – sublingual 5-10mg, orally 30-120mg. IV infusion 2-10mg/hr.

KEY POINTS – NITRATE VASODILATORS

1. Glyceryl trinitrate tablets must be given sublingually as the drug is inactivated if swallowed
2. Tablets must be kept in glass air-tight containers and rejected if more than two months old
3. Postural hypotension may limit treatment
4. Patches may be applied to a hairless skin area where little movement occurs, and replaced daily at a slightly different site
5. Isosorbide mono/dinitrate is more stable and can be used for prophylaxis
6. Tolerance may occur, reduced by giving low doses or by temporary removal of skin patch

POTASSIUM CHANNEL ACTIVATORS

Nicorandil has both arterial and venous vasodilating properties and is licensed for the prevention and long term treatment of angina. Decreased peripheral resistance, decreased pre-load, dilates epicardial and subendocardial coronary vessels.

Nicorandil – caution with hypovolaemia, low BP, acute pulmonary oedema and myocardial infarction. Side effects include headache, flushing, N&V, myalgia, dizziness and weakness. Dose 10mg twice daily, headache decrease to 5mg twice daily. Up to 30mg twice daily.

Ca⁺⁺ CHANNEL BLOCKERS

These drugs interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence myocardial cells, cells within the specialised conducting system of the heart and the cells of vascular smooth muscle. Myocardial contractility may be reduced, formation and propagation of electrical impulses within the heart may be depressed. Verapamil, diltiazem differ from the dihydropyridine calcium channel blockers (amlodipine, felodipine, nifedipine and nimodipine).

Avoid verap/dilt in heart failure.

Amlodipine – does not reduce myocardial contractility or produce heart failure. Longer duration of action. Flushing and headache. Beware hepatic impairment. Contraindicated in hypotension, unstable angina, aortic stenosis. Can cause sweating, palpitations, jaundice and blood disorders. 5mg daily to maxm 10mg.

Diltiazem – longer acting for hypertension. Use in patients where beta blockers are contraindicated or ineffective. Less negative inotropic effect than verapamil. Beware liver and renal impairment, heart failure and bradycardia. Contraindicated in heart block. 60mg TDS, elderly BD to maxm 360mg daily.

Felodipine - does not reduce myocardial contractility or produce heart failure. Longer duration of action. Flushing and headache. Avoid grapefruit juice. Contraindicated in unstable angina and heart failure. Aortic stenosis. Within one month of MI. 5mg, elderly 2.5mg daily. Maintenance 5-10mg daily.

Nifedipine – relaxes vascular smooth muscle and dilates coronary and peripheral arteries. Less myocardial and anti-arrhythmic activity. Less chance of heart failure. Flushing and headache. Same as felodipine. 5mg TDS up to 20mg TDS.

Verapamil – used in the treatment of angina, hypertension and arrhythmias. Highly negatively inotropic and reduces cardiac output, slows heart rate and may impair AV conduction. May precipitate heart failure, exacerbate conduction disorders and cause hypotension. Should not be used with or after beta blockers. Constipation common. Contraindicated in hypotension, bradycardia, heart block, WPW and heart failure. 40-120mg TDS for arrhythmias, 80-120mg TDS angina, 240-480mg 2 to 3 times a day hypertension. Slow IV over 2 minutes 5-10mg.

Nimodipine – smooth muscle relaxant effect mainly on cerebral arteries. Prevents vascular spasm following subarachnoid haemorrhage. Caution with cerebral oedema or raised ICP. 60mg every 4 hours orally within 4 days of subarachnoid haemorrhage and continue for 21 days. IV infusion 1mg/hr in central line, up to 2mg/hr after 2 hrs.

KEY POINTS – CALCIUM CHANNEL BLOCKERS

1. Some are used in angina, others in hypertension, as they differ in their pattern of activity
2. Not indicated in heart failure, may cause further deterioration
3. Nimodipine is exceptional in its use in subarachnoid haemorrhage
4. Long acting products must not be regarded as interchangeable

PERIPHERAL VASODILATORS

Naftidrofuryl – used in intermittent claudication. Alleviates symptoms and improves pain free walking. Assess after 3-6 months. Can cause epigastric pain, nausea, rash and liver problems. Peripheral vascular disease 100-200mg TDS, cerebral vascular disease 100mg TDS.

NICE GUIDELINES HYPERTENSION

Blood Pressure 140/90 or above, return to two subsequent clinics. Lifestyle changes – exercise, diet, relaxation therapy, reduce stress, reduce alcohol intake, reduce coffee consumption, decrease salt intake, stop smoking. Identify CVS risk – tests for diabetes, damage to heart/kidneys.

Aim is to reduce blood pressure to 140/90 or below

Blood pressure persistently above 160/100; 140/90 with CVS risk; 55 years old+ or black patient – first choice pharmacological intervention calcium channel blocker or thiazide diuretic; younger than 55 years old – ACE inhibitor (or angiotensin II receptor antagonist if ACE not tolerated)

If second hypotensive needed – add ACE to calcium channel blocker or vice versa in younger patient

If three hypotensives required – ACE+calcium channel blocker+thiazide diuretic

If fourth drug required – consider higher dose thiazide, beta blocker, selective alpha blocker

Blood pressure >180/110, papilloedema, retinal haemorrhage – refer immediately

DRUGS THAT CAUSE QT PROLONGATION

If the QT interval is prolonged, the ventricular contraction sequence is severely disrupted, leading to a characteristic ECG trace of atypical ventricular dysrhythmia called torsade de pointes. Syncope, collapse and even death can result. Patients with a pre-existing problem can be put at risk with the following drugs:-

Cardiac drugs – amiodarone, sotalol, disopyramide, procainamide

Antibacterials – erythromycin, clarithromycin, moxifloxacin, pentamidine

Calcium channel blockers – diltiazem, verapamil

Antipsychotics – phenothiazines, haloperidol, pimozide, sertindole, amisulpride

Anti-depressants – TCA's, fluvoxamine, paroxetine, lithium

Anti-emetics – domperidone

Anti-fungals – ketoconazole

Anti-histamines – mizolastine

Analgesics - methadone

SYMPATHOMIMETICS

This group of drugs vary according to whether they act on alpha or beta adrenergic receptors. Beta₁ increases both heart rate and contractility; beta₂ vasodilatation; alpha vasoconstriction. Dobutamine and dopamine act on beta₁ receptors in cardiac muscle, increasing contractility and having little effect on rate. Low dose dopamine causes vasodilatation and increases renal perfusion; high dose (5mcg/kg/min) lead to vasoconstriction. Dopexamine acts on beta₂ receptors in cardiac muscle producing a positive inotropic effect and on peripheral receptors to increase renal perfusion. Isoprenaline is less selective and increases both heart rate and contractility. Vasoconstrictors raise blood pressure by constricting peripheral vessels. They can do so at the expense of vital organs such as the kidney. Ephedrine raises heart rate as well. If hypotension occurs with tachycardia then a pure alpha stimulator such as methoxamine is useful.

Dobutamine – use when inotropic support is needed – shock, MI etc. Beware when severe hypotension complicating cardiogenic shock. May get tachycardia and marked rises in systolic pressure. IV infusion at 2.5-10mcg/kg/min.

Dopamine – same indications. Always correct hypovolaemia and use low dose in cardiogenic shock. Do not use in tachyarrhythmias or phaeochromocytoma. Can cause N&V, peripheral vasoconstriction, hypotension, hypertension and tachycardia. Infuse at 2-5mcg/kg/min.

Isoprenaline – indicated in heart block and severe bradycardia. Beware in ischaemic heart disease, diabetes mellitus and hyperthyroidism. Can cause arrhythmias (inc tachy), hypotension, tremor and headache. IV infusion at 0.5-10 mcg/min.

Noradrenaline – beware any thrombosis, angina, hyperthyroidism, hypervolaemia, diabetes. Contraindicated in hypertension. Can cause peripheral ischaemia as well as bradycardia, arrhythmias. Acute hypotension by IV infusion through central line at 0.16-0.33ml/min (soln 80mcg/ml). Cardiac arrest 0.5-0.75ml (soln 200mcg/ml) by rapid IV injection.

KEY POINTS – SYMPATHOMIMETICS

1. Different agents may act more or less selectively on different receptors
2. Type of response varies accordingly
3. Injection of inotropic sympathomimetics (dobutamine, dopamine, dopexamine) requires care, as the response may vary markedly with an increase in dose
4. Vasoconstrictor sympathomimetics now used less frequently in shock

ANTI-PLATELET AGENTS

Decrease platelet aggregation and may inhibit thrombus formation in arterial circulation. Low dose aspirin is used for primary and secondary prevention of thrombotic cerebrovascular or cardiovascular disease. Clopidogrel is licensed for acute coronary syndrome without ST elevation. Dipyrimadole used as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. Abciximab is a monoclonal antibody which binds to the receptors. Should be considered in the management of unstable angina or non-ST-segment elevation myocardial infarction and an adjunct to percutaneous coronary intervention.

Abciximab – caution measure baseline PT, APTT, platelets at 2-4hrs and 24hrs, Hb and haematocrit at 12 and 24hrs. Contraindications – active bleeding, stroke within 2yrs, trauma within 2 months. Side effects – bleeding, N&V, hypotension, bradycardia, chest pain, back pain, headache. Dose IV injection over 1 minute, 250 micrograms/kg followed by infusion 125 nanograms/kg/minute (maxm 10 micrograms/min). Start 10-60mins before percutaneous coronary intervention and continue infusion for 12hrs.

Aspirin – caution asthma, pregnancy, uncontrolled hypertension. Contraindications – children under 16yrs and breast feeding, active peptic ulceration, bleeding disorders. Side effects – bronchospasm, bleeding. Dose 150-300mg after ischaemic episode. Maintenance 75-150mg/day.

Clopidogrel – prevention of atherosclerotic events in peripheral vascular disease or within 35 days of myocardial infarction or within 6 months of ischaemic stroke or in acute coronary syndrome without ST segment elevation (with aspirin). Avoid first few days after MI and 7 days after ischaemic stroke. Stop 7 days prior to surgery. Side effects – bleeding, abdominal discomfort, N&V. Dose 75mg daily. Acute coronary syndrome 300mg then 75mg daily.

Dipyrimadole – caution in worsening angina, aortic stenosis, MI, heart failure. Side effects - GIT upset, headache, dizziness, myalgia, hypotension. Dose 300-600mg daily in divided dose 3-4 times a day.

ANTICOAGULANTS

Prevention of thrombus formation or extension of existing thrombus, in a vein where the thrombus consists of a fibrin web enmeshed with platelets and red cells. Prevention and treatment of deep vein thrombosis (DVT) in the legs. Less use in arterial thrombosis or where clots contain little fibrin. Used to prevent thrombus formation on prosthetic heart valves. Heparin initiates anticoagulation quickly but has short duration. This is different to the low molecular weight heparins which have a longer duration of action. Initial treatment with IV loading dose followed by infusion at the same time as commencing oral anticoagulants such as warfarin. 3 days for orals to take effect. Measure APTT daily. Low dose heparin is used for prophylaxis. If haemorrhage occurs reverse with protamine sulphate.

Heparin – beware renal and liver failure, epidural and spinal anaesthetic. Can cause thrombocytopenia (monitor) and hyperkalaemia (inhibits aldosterone secretion). Avoid in haemophilia, thrombocytopenia, peptic ulcer, recent CVA. Can cause haemorrhage. DVT treatment IV load 5000 units followed by 15-25units/kg/hr or SC 15000 units every 12hrs. Prophylaxis in general surgery 5000 units 2hrs before surgery then every 8-12 hrs for 7 days.

Enoxaparin – (Clexane) low molecular weight heparin. Effective in prevention of DVT. Long duration, therefore once daily by SC injection. Same problems as heparin. Dose 20mg 2hrs before surgery then every 24hrs (7-10 days). Double dose for high risk.

Dalteparin - (Fragmin) low molecular weight heparin. Effective in prevention of DVT. Long duration, therefore once daily by SC injection. Same problems as heparin. Dose 2500 units 2hrs before surgery then daily for 5-7 days. Double dose for high risk.

Warfarin – antagonises effect of vitamin K, takes 48-72hrs for effect to develop. Used in DVT, pulmonary embolus and heart prosthesis. 10mg daily for 2 days then follow prothrombin time (INR). Maintenance is 3-9mg daily. Prophylaxis for DVT aim for INR 2-2.5, treatment DVT, PE or AF - INR 2.5, prosthetic heart valves and recurrent DVT/PE aim for INR of 3.5. INR on alternate days initially, then every 12 weeks. Major bleeding give vitamin K 5mg by slow IV injection and Fresh Frozen Plasma (FFP) 15ml/kg.

KEY POINTS – HEPARIN

1. Standard heparin is given by IV or SC injection under laboratory control
2. Fractionated or low molecular weight heparins are for SC injection only
3. They have a longer action that permits single daily doses – laboratory control is not necessary
4. Effects of heparin can be neutralised rapidly by an injection of protamine

KEY POINTS – ORAL ANTICOAGULANTS

1. Dose should be taken same time every day to avoid changes in the blood levels of anticoagulant
2. Clotting times must be closely monitored
3. Observe any unusual bleeding or bruising – nose, gums, periods or tarry stools
4. Patients should be advised not to make any substantial alterations in their diet
5. Alcoholic beverages are best avoided, may reduce the absorption of vitamin K
6. Patients should be advised to avoid aspirin and not to take any other non-prescribed product without reference to their doctor
7. Patients must always carry some indication that they are taking an anticoagulant and inform their dentist before treatment

FIBRINOLYTIC

Activate plasminogen to form plasmin which degrades fibrin. Streptokinase is used in life threatening situations. Reduces mortality in MI. Risk of bleeding. Avoid in recent surgery, haemorrhage, CVA, peptic ulcer. N&V, arrhythmias (used in MI), hypotension, bleeding. Allergic reaction flushing, rash and uveitis.

Streptokinase – use in DVT, PE, acute arterial thrombosis. IV infusion 250000 units over 30 mins then 100000 units every hour for up to 12-72 hrs. MI 1500000 units over 60 mins.

Alteplase – within 6hrs of MI 15mg IV followed by infusion 50mg over 30mins, then 35mg over 60mins (total 100mg over 90mins). Within 6-12hrs of MI 10mg followed by 50mg over 60mins then four infusions each of 10mg over 30mins (100mg over 3hrs). Pulmonary embolus 10mg IV over 1-2mins followed by infusion of 90mg over 2hrs.

STATINS

Competitively inhibit HMG CoA reductase, an enzyme involved in cholesterol synthesis, especially in the liver. Effective in lowering LDL-cholesterol but less effective in reducing triglycerides and raising HDL-

cholesterol. Reduce coronary events in patients with a history of angina. Aim to achieve target total cholesterol concn of 5mmol/L. Beware liver disease and high alcohol intake. Monitor LFT's. Can cause reversible myositis, headache, GIT disturbance.

Atorvastatin – primary hypercholesterolaemia. Also can cause reversible myositis, peripheral neuropathy, pruritis, impotence, thrombocytopaenia. 10mg daily, increasing to 40mg daily if required (maxm 80mg).

Simvastatin - primary hypercholesterolaemia. Alopecia, dizziness, pancreatitis. 10mg daily at night, adjusting every four weeks up to 80mg daily.

Pravastatin - primary hypercholesterolaemia with no response to diet, reduce ischaemic events. Dose 10-40mg at night

To decrease triglycerides as well as LDL cholesterol, raising HDL cholesterol – fibrates such as bezafibrate and gemfibrozil. Risk of myositis which is increased if used with statin.

Bezafibrate – hyperlipidaemias IIa, IIb, III, IV and V. Contraindications – liver impairment, pregnancy, breast feeding. Side effects – GIT upset, pruritis, urticaria, headache, dizziness, hair loss. Dose 200mg TDS after meals.

Gemfibrozil – similar profile. Dose 1.2g daily, in two divided doses.

HAEMATOLOGY

Treatment of iron deficiency anaemia should not commence until underlying causes have been excluded. Prophylaxis in pregnancy only when additional risk factors present, menorrhagia, after gastrectomy.

Iron – oral iron in the ferrous form is better absorb. 100-200mg daily. Haemoglobin concentration should rise by 2g% over 3-4 weeks. Once in normal range continue for further 3 months to replenish stores. Parental iron when compliance poor, renal failure on EPO. Iron sucrose by slow intravenous infusion.

Desferrioxamine – used in iron overload, iron chelating compound. Subcutaneous infusion over 8-12hrs, 3-7 times a week. Dose reflects the amount of overload. Can cause hypotension, hearing and visual disturbance, GIT disturbance, fever, headache, arthralgia.

Megaloblastic anaemias are due to lack of vitamin B12 or folate. Pernicious anaemia is malabsorption of vitamin B12 – autoimmune.

Hydroxocobalamin - can be given at intervals of three months for maintenance therapy. Deep IM injection 1mg three times a week for 2 weeks then 1mg every three months. Can cause itching, fever, chills, hypokalaemia.

Folic acid – should never be given alone for pernicious anaemia – may precipitate sub-acute combined degeneration of the spinal cord. Dose 5mg daily for 4 months orally then 5mg every 1-7 days depending on underlying cause.

Erythropoetin – used in chronic renal failure and those with anaemia caused by cytotoxic chemotherapy. IV injection over 5 minutes – 5units/kg three times weekly adjusted according to response in steps of 25units/kg three times weekly at intervals of at least four weeks. Maintenance usually 25-100units/kg three times weekly. Can cause increase in blood pressure, seizures, hyperkalaemia, skin reactions.

DRUGS RELATED TO THE GASTRO-INTESTINAL TRACT

ULCER-HEALING

Peptic ulceration commonly involves the stomach, duodenum and lower oesophagus. Those not caused by NSAID's are usually caused by Helicobacter pylori. One week of triple therapy regimen including proton pump inhibitor eradicate bacteria in 90% cases. Amoxicillin and clarithromycin initially, failure use amoxicillin and metronidazole. Proton pump inhibitor can be used with NSAID's.

H2 receptor antagonists – heal gastric and duodenal ulcers by reducing acid output. Useful in reflux and in higher doses for Zollinger-Ellison syndrome. Maintenance in only those with recurrences. Beware liver disease and renal impairment. GIT disturbance and diarrhoea, headache and dizziness. Interaction with warfarin, phenytoin and theophylline.

Cimetidine – ulcer and reflux treatment. Alopecia, tachycardia, interstitial nephritis. 400mg twice daily or 800mg at night for at least four weeks, 8 weeks when NSAID's.

Ranitidine – similar plus visual disturbance, erythema multiforme. 150mg BD or 300mg nocte for 4-8 weeks, in NSAID induced ulcers double dose.

Proton pump inhibitors – inhibit gastric acid by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the proton pump) of the gastric parietal cell. Effective, short term treatment for ulcers. Useful in treatment of NSAID induced ulcers and Zollinger-Ellison syndrome. Beware liver disease. May mask gastric carcinoma. GIT disturbance, headache, pruritis, hypersensitivity reactions.

Omeprazole – reflux where symptoms are severe. NSAID associated ulceration where NSAID's are essential. Can cause bullous eruptions, toxic epidermal necrolysis, vertigo, somnolence, insomnia, liver dysfunction, blood disorders. 20mg daily for 4 weeks, 8 weeks when severe. Maintenance for recurrent ulceration 20mg once daily. Same for NSAID's. IV over 5 minutes for reduction during anaesthesia – 40mg one hour before surgery.

Lansoprazole – similar to omeprazole. 30mg daily for 8 weeks. NSAID's 15-30mg daily for 4 weeks.

Rabeprazole – benign gastric ulcer 20mg daily in the morning for 6 weeks followed by further 6 weeks if necessary. Duodenal ulcer 20mg daily for 4 weeks followed by further 4 weeks if necessary.

KEY POINTS – ULCER HEALING DRUGS

1. Malignancy should be excluded before starting treatment in elderly patients
2. Treatment with H₂ receptor antagonists is basically symptomatic, not curative
3. Extended maintenance treatment necessary
4. Cimetidine increases plasma levels of warfarin, phenytoin, theophylline and any other drugs by inhibiting their metabolism
5. Proton pump inhibitors have a similar influence
6. Prostaglandin derivatives have a protective action by promoting mucus production

ACUTE DIARRHOEA

Prevention followed by rehydration. Antimotility drugs relieve the symptoms of diarrhoea. Not for use in children.

Codeine phosphate – not for children. Contraindicated in abdominal distension, acute ulcerative colitis and antibiotic-associated colitis. 30mg 3-4 times a day

Loperamide – adults and children over 4yrs. Contraindicated in abdominal distension, acute ulcerative colitis and antibiotic-associated colitis. Side effects – cramps, dizziness, drowsiness, urticaria, ileus and bloating. Dose – 4mg initially followed by 2mg after each loose stool for up to 5 days (maxm 16mg daily). Chronic diarrhoea 4-8mg daily in divided doses.

Colestyramine – diarrhoea associated with Crohn's disease, ileal resection, vagotomy and diabetic neuropathy. Dose – 12-24grams daily in 1-4 divided doses to a maxm 36grams daily.

LAXATIVES

Bulk forming laxatives increase faecal mass. Balanced diet with adequate hydration.

Fybogel – contraindicated in intestinal obstruction, dysphagia, colonic atony and impaction. Dose – one sachet twice a day

Stimulant laxatives increase intestinal motility causing cramps. Avoid in obstruction. Can cause hypokalaemia and atonic colon with prolonged use.

Senna – dose 2-4 tablets (7.5mg) at night

Sodium picosulfate – 5-10mg at night

Bisacodyl – tablets take 12 hours to work, suppositories 20-60 minutes. Oral - 5-10mg at night up to 15-20mg. Suppositories – 10mg in morning

Codanthramer – carcinogenic in rats. Terminally ill only. 1-2 capsules at bedtime.

INFLAMMATORY BOWEL DISEASE

Effective management includes drug therapy, nutrition and surgery. Aminosalicylates and steroids form the basis of treatment. Local preps are available for rectal disease. IV steroids may be required for severe disease. Failure to respond can allow the use of ciclosporin or methotrexate for a short course. If abscess formation is a problem, metronidazole should be used. Aminosalicylates are useful in remission with UC but not in Crohn's. Azathioprine can be used in relapsing cases. The aminosalicylates can still cause blood disorders and lupoid phenomenon. Do not use in aspirin sensitive patients or those with renal impairment. Can cause diarrhoea, nausea, headaches, urticaria, pancreatitis, hepatitis and blood disorders.

Mesalazine – mild to moderate UC and maintenance of remission. Acute attack 2400mg daily in divided doses, maintenance of remission 1200-2400mg daily (Asacol). Avoid if GFR <50ml/min. Also can cause allergic myocarditis and lung reactions.

Sulfasalazine – UC and Crohn's. Not in patients with sulphonamide sensitivity. Similar side effect profile with hallucinations, depression, insomnia, alopecia, tinnitus, renal problems, orange urine, soft contact lenses stained orange. Digoxin absorption impaired. Reversible male infertility. Dose 1-2grams QDS until remission. Maintenance 500mg QDS

Azathioprine – metabolised to mercaptopurine and dose should be reduced if on allopurinol. Can develop myelosuppression and hepatic toxicity. Monitor FBC weekly initially. Side effects – malaise, dizziness, vomiting, diarrhoea, jaundice, myalgia, nephritis, marrow suppression. Dose 1-3mg/kg daily orally or IV.

PHOSPHATE-BINDING AGENTS

Aluminium and calcium containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia which complicates renal failure. Calcium containing drugs are contraindicated in hypercalcaemia and hypercalcuria. Aluminium containing drugs may increase plasma levels of aluminium in dialysis patients.

Aluminium hydroxide – 475mg, divided dose with meals. According to requirements.

Calcium carbonate – 420mg, according to requirements

Sevelamer – 2.4 to 4.8gms daily in divided doses with meals.