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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Acetylsalicylic acid (ASA, aspirin)

Overview • Aspirin works by blocking the action of both cyclooxygenase-1 and 2. • Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis. • Cyclo-oxygenase is an enzyme that converts arachidonic acid to thromboxane A2 (TXA2), a strong platelet agonist • Because the platelet has no protein synthetic apparatus the effects of aspirin are irreversible and last for the life of the platelet (8-10 days) • ↑ bleeding time (PT and PTT unchanged) • The blocking of thromboxane A2 formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease. • Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case. Mechanism of action • ASA covalently attaches an acetyl group to COX. • Irreversible COX-1 inhibition → inhibition of thromboxane (TXA2) synthesis in platelets → inhibition of platelet aggregation (antithrombotic effect) • Onset of antiplatelet action: within minutes • Duration of antiplatelet action: 7–10 days • Irreversible COX-1 and COX-2 inhibition → inhibition of prostacyclin and prostaglandin synthesis → antipyretic, anti-inflammatory, and analgesic effect Effects • Low dose (below 300 mg/day): inhibition of platelet aggregation • Intermediate dose (300-2400 mg/day): antipyretic and analgesic effect • High dose (2400-4000 mg/day): anti-inflammatory effect

What do the current guidelines recommend? • first-line for patients with ischaemic heart disease • Current NICE guidelines advise that people with acute upper gastrointestinal bleeding who take aspirin for secondary prevention of vascular events and in whom haemostasis has been achieved continue on low dose aspirin. • the U.S. Preventive Services Task Force (USPSTF), recommended that, for some people, aspirin can be used to help reduce their risk of cardiovascular disease and colorectal cancer. Potentiates • oral hypoglycaemics • warfarin • steroids

Reye syndrome

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• Definition: a rare type of hepatic encephalopathy that is associated with aspirin use for viral illness in children < 19 years • Aetiology: aspirin use in individuals < 19 years of age with a febrile illness • Pathophysiology accumulation of salicylate metabolites in the liver → mitochondrial injury and reversible inhibition of enzymes required for fatty acid oxidation; acute encephalopathy Hyperammonemia → cerebral edema → ↑ ICP • Features Preceding viral infection (e.g., influenza, varicella or viral gastroenteritis) Acute encephalopathy Severe vomiting coma Liver failure Fatty degeneration Hepatomegaly • Diagnostics: clinical diagnosis; further testing to rule out other causes (diagnosis of exclusion) ↑ AST and ALT Hyperammonemia Hypoglycemia Liver biopsy: microvesicular hepatic steatosis • Prevention Aspirin should be avoided in individuals < 19 years of age Exception: children with Kawasaki disease • Prognosis →Mortality rate: ~ 20%

In hypersensitive patients aspirin can cause: • Angioedema • Bronchospasm, and • Urticaria (skin rashes).

ASA can be continued normally if patient is going for dental procedure

Aspirin is not considered to be safe in breast-feeding due to the risk of causing Reye's syndrome in the baby.

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Salicylate overdose

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose.
The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis.

Tinnitus is characteristic and salicylate toxicity may produce deafness. Overview • A key concept for the exam is to understand that salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis.
 Early stimulation of the respiratory centre leads to a respiratory alkalosis
 later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.
• The metabolic acidosis can increase the transfer of salicylates across the blood-brain barrier, thereby increasing CNS toxicity Features • Early features: hyperventilation (centrally stimulates respiration) respiratory alkalosis the most prominent feature of the early period after aspirin overdose tinnitus: typically occurs at plasma salicylate concentrations above 400-500 mg/l vertigo lethargy sweating, pyrexia
 salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production peripheral vasodilatation and bounding pulse

 nausea/vomiting → dehydration • Later features: metabolic acidosis by uncoupling oxidative phosphorylation, leading to a build- up of organic acids in the blood. hyperglycaemia and hypoglycaemia
 Hypoglycaemia is commonly seen in children but not in adults seizures coma Although decreased consciousness is seen in aspirin overdose, it is seen late, and is associated with severe metabolic acidosis and hypokalaemia. Early presentation with coma will suggest that another drug has been taken in addition to aspirin.

Treatment • No specific antidote
• The management is supportive, with measures to prevent further absorption from the gastrointestinal tract and enhance excretion.
• General (ABC, charcoal) Multi-dose activated charcoal may be indicated

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 activated charcoal should be repeated as bezoars may form, resulting in delayed absorption of salicylate. This should continue until salicylate levels have peaked. • Urinary alkalinization alkalinisation of the urine should be considered in patients with a plasma level > 300 mg/L. urine and serum alkalinization through intravenous sodium bicarbonate (1.25% or 8.4%) By alkalinizing the urine, charged salicylic acid will become protein bound and secreted through the proximal tubule, which minimizes the diffusion of uncharged salicylate back into the renal epithelium.
 The ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment.
 The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold. Alkalinization of the serum further promotes diffusion of salicylate out of the brain. • Haemodialysis Indications for haemodialysis in salicylate overdose serum concentration > 700mg/L metabolic acidosis resistant to treatment acute renal failure pulmonary oedema neurological impairment (coma, hallucinations or seizures)

Clopidogrel Most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

• Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease.
• Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include: prasugrel ticagrelor ticlopidine Mechanism (Inhibition of the platelet ADP receptor) • antagonist of the P2Y12 adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets Indications • clopidogrel is used in addition to aspirin in patients with an acute coronary syndrome. The dose is 300 mg.
• NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease.
• Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole Interactions • concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009) • this advice was updated by the MHRA in April 2010, evidence seems inconsistent but

omeprazole and esomeprazole still cause for concern. Other PPIs such as lansoprazole should be OK

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Clopidogrel • action → antagonist of the P2Y12 adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets • other members of the same class (thienopyridines): prasugrel ticagrelor ticlopidine • Indications → 1st line for : ACS , an ischaemic stroke , TIA and peripheral arterial disease.
• Interaction → most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

Prasugrel
• a third-generation thienopyridine antiplatelet agent • ADP receptor inhibitors • advantages compared with clopidogrel faster onset of action, greater potency in the inhibition of adenosine-induced platelet aggregation, more consistent antiplatelet response • Prasugrel is contra-indicated in patients with prior transient ischaemic attack or stroke.
 In the TRITON-TIMI 38 trial, patients in this group had a higher rate of stroke when taking Prasugrel compared with those taking Clopidogrel.

IIb/IIIa inhibitors (eg: Abciximab) • Other members of this drug group
 abciximab eptifibatide tirofiban • Action monoclonal antibody antagonizes IIb/IIIa glycoprotein receptor on activated platelets • prevents platelet aggregation • Abciximab is a humanised monoclonal antibody

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Phosphodiesterase III (PDE) inhibitors (dipyridamole & cilostazol)

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Mechanism of action • inhibits phosphodiesterase → increase platelet cAMP (due to decreased breakdown of cAMP) → reduce intracellular calcium levels → inhibition of platelet aggregation. • direct arterial vasodilation inhibits cellular uptake of adenosine → more available to act on coronary vessels → vasodilation • inhibition of thromboxane synthase

Indications • Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack • Cilostazol is currently licensed for the management of patients with intermittent claudication without rest pain and with no signs of tissue necrosis.
 It is a first-line medication for the treatment of claudication caused by peripheral artery disease (PAD).
 Trials show an improvement in time to initial pain on walking and maximal walking distance when compared to placebo. metabolised by cytochrome P450 3A4. Contraindications • known

bleeding tendencies (e.g. active peptic ulcer disease, previous haemorrhagic stroke in the last 6 months).
• Asthmatics (may provoke bronchospasm)

Angiotensin-converting enzyme (ACE) inhibitors
Mechanism of action • Inhibit the conversion angiotensin I to angiotensin II Indications • hypertension
 first-line treatment in younger patients with hypertension and are also extensively used to treat
 less effective in treating hypertensive Afro-Caribbean patients.
• diabetic nephropathy
• heart failure. • secondary prevention of IHD. Side-effects • Cough:
 occurs in around 15% of patients
 may occur up to a year after starting treatment. Thought to be due to increased bradykinin levels The enzyme ACE is also responsible for the metabolism of bradykinin in mast cells and ACEi leads to its bradykinin accumulation
 This phenomenon is not seen in subjects taking angiotensin receptor blockers such as losartan. • Angioedema:
 may occur up to a year after starting treatment ACE inhibitors are the most common cause of drug-induced angioedema

(swelling of his lips and tongue) • Hyperkalaemia • ACEi dilate the efferent arteriole of the glomerulus, ↓GFR ↑ creatinine and BUN. • 1st-dose hypotension: more common in patients taking diuretics Cautions and contraindications • Pregnancy and breastfeeding – avoid (ACEi & ARB renal dysgenesis in the fetus) Exposure to ACE inhibitors in the first trimester showed a significant increase in major (in particular, cardiovascular) congenital malformation. • Renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis • Aortic stenosis - may result in hypotension • Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - signficantly increases the risk of hypotension • Hereditary of idiopathic angioedema • The co-administration of a potassium-sparing diuretic and an ACE inhibitor, may result in profound hyperkalaemia. Thus patients on both these drugs should have their potassium monitored closely. Monitoring • Urea and electrolytes should be checked before treatment is initiated and after increasing dose Monitoring of renal function and potassium is important after commencement of an ACE inhibitor. The optimum period to check this is one to two weeks after commencing the medication. • A rise in the creatinine and potassium may be expected after starting ACE inhibitors.
 Acceptable increases are an increase in serum creatinine, up to 50% from baseline or up to 265µmol/l (whichever is smaller) and an increase in potassium up to 5.5 mmol/l. NICE guidelines state that when initiating ACE inhibitor therapy a 25% reduction in the eGFR or 30% increase in the serum creatinine is tolerable and should not lead to changes in dosing. ACE inhibitors should also be stopped or dose adjusted if is there is a rise in the serum potassium level to greater than 6 mmol/l. Other causes of a deterioration in renal function should be excluded first before stopping the ACE inhibitor.

 e.g: patient taking trimethoprim
 This drug competes with creatinine for excretion in the nephron ↑ serum creatinine.
 the appropriate option would be to re-check the blood tests in one to two weeks once trimethoprim has been discontinued to see whether the level of renal dysfunction is sustained or improves. Usage of ACEi & ARB as combination (NICE January 2015)
• Do not combine an ACE inhibitor with an ARB to treat hypertension.
• no significant benefits of ACEi & ARB combination were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function.
• The NICE guideline on chronic heart failure recommends that, after seeking specialist advice, the addition of an ARB licensed for heart failure is an option that could be considered for people who remain symptomatic despite optimal therapy with an ACE

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 Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.

direct renin inhibitors • Aliskiren (branded as Rasilez) Direct renin inhibitor
• Action: by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I • indication: only current role would seem to be in patients who are intolerant of more established antihypertensive drugs • no trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists • adverse effects were uncommon in trials although diarrhoea was occasionally seen Other notes
• Enalapril is a prodrug for enalaprat, the active agent • irbesartan : the dose response is linear, as such dose can be titrated more easily from a base of 75 mg to a maximum of 300 mg.

Adrenoceptor antagonists Doxazosin is an α-1 adrenoceptor antagonist used in the treatment of hypertension and benign prostatic hypertrophy

Alpha antagonists • alpha-1: doxazosin cause orthostatic hypotension • alpha-1a: tamsulosin - acts mainly on urogenital tract • alpha-2: yohimbine • non-selective: phenoxybenzamine (previously used in peripheral arterial disease) Phenoxybenzamine presurgical management of hypertension in phaeochromocytoma. Beta antagonists
• beta-1: atenolol • non-selective: propranolol Carvedilol and labetalol are mixed alpha and beta antagonists

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Beta-blockers

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Indications • angina • post-myocardial infarction • Heart failure: there is now strong evidence that certain beta-blockers improve both symptoms and mortality. Especially Bisoprolol • arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation • hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction. • thyrotoxicosis • migraine prophylaxis • anxiety Beta- blocker in heart failure • NICE recommends β blockers in all HF patients. • In chronic obstructive pulmonary disease (COPD) patients with HF, cardioselective β blockers appear safer at lower doses than higher doses or non-selective β blockers. • Bisoprolol 5 mgs is too high an initial starting dose, a low dose can always be titrated up later, if tolerated. (starting dose Bisoprolol 1.25 mg od) • Carvedilol though effective treatment for heart failure is not selective and therefore carries a greater risk of causing bronchospasm. • Atenolol though cardioselective has no clinical evidence for prognostic benefit in heart failure. • The patient should be closely monitored for deterioration in lung function postadministration. Examples • Atenolol Atenolol is a water soluble beta-blocker,

 taken once daily

 not associated with drowsiness/sleep disturbance like the lipid-soluble beta-blockers. • Propranolol one of the first beta-blockers to be developed.

 Lipid soluble therefore crosses the blood-brain barrier • Nebivolol

 has a vasodilatory action in addition to β-blocking effects

 associated with a lower incidence of erectile dysfunction compared with other βblocking agents • Bisoprolol → the most cardio-selective beta-blocker • Metoprolol The most lipid-soluble and therefore has the largest volume of distribution

 ↑lipid solubility → greater penetration across the blood-brain barrier (and also into other tissues), and therefore a greater incidence of night terrors Maximal gastrointestinal absorption of drugs occurs when there is intermediate lipid and water solubility, so that drugs with greater lipid solubility, although allowing greater tissue penetration, may be more poorly absorbed Metoprolol though selective is shorter acting. • Oxprenolol → has an intrinsic sympathomimetic properties.

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Carvedilol
Bisoprolol Not β1- selective
Highly β1- selective
Vasodilatation due to α-1- blockade No α-1- blocking activity Lipids effects Positive lipid effect ↑↑HDL & ↓↓LDL Negative lipid effect ↑↑ cholesterol , TG, VLDL Lipid profile almost not affected Oral bioavailability of digoxin increased
No interaction with other CV drugs known Sensitive to liver enzyme induction
Not sensitive to liver enzyme induction Extensive metabolism in the liver (CYP2D6)(dose adjustment in liver impairment) No dose adjustment required

Side-effects • bronchospasm • cold peripheries • β-Blockers cause a rise in peripheral vascular resistance due to the unopposed αadrenoceptor effects (vasoconstriction) • Fatigue

 fatigue is a frequent side effect
 typically is felt two hours and beyond after taking the drug. • sleep disturbances, including nightmares • β-blockers associated with increased dreams/possible night terrors Contraindications • uncontrolled heart failure • asthma • sick sinus syndrome • concurrent verapamil use: may precipitate severe bradycardia • There is a theoretical risk of intrauterine growth retardation with the use of atenolol in pregnancy although the studies which showed this effect were done with very large doses of atenolol. Beta-blocker overdose

Features • bradycardia • hypotension • heart failure • syncope Management • if bradycardic then atropine • in resistant cases glucagon may be used • Glucagon acts by bypassing the blocked β-receptor, thus activating adenyl cyclase formation of cyclic AMP from ATP. Cyclic AMP in turn exerts a direct stimulant action on the heart.
• The action of glucagon, essential for reversing the effect of beta-blocker overdose Promotes the formation of cyclic AMP. Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, with a bolus of 3-10 mg being required, then 25 mg/hr by infusion. • Haemodialysis is not effective in beta-blocker overdose

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Calcium channel blockers

• Voltage-gated calcium channels are present in:

1. myocardial cells,
2. cells of the conduction system and
3. cells of the vascular smooth muscle.
   (they have no effect on veins).
   • The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

Examples Indications & notes Verapamil • Angina, hypertension, arrhythmias
• Highly negatively inotropic • Should not be given with beta-blockers as may cause heart block Diltiazem • Angina, hypertension
• Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers Nifedipine, amlodipine, felodipine (dihydropyridines) • Hypertension, angina, Raynaud's • Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure • What is the conventional cardiac micro-anatomical structure targeted by calciumchannel blockers? L-type calcium channels all conventional calcium-channel blockers work on L-type calcium channels The L-type channels are found on a tubular network of invaginations of sarcolemma of muscle fibres called T (transverse) tubules. T tubules contain 2 main types of calcium channels: L-type calcium channels (where calcium channel blocker do interact) T (transient) type calcium channels (conventional calcium channel blockers have no effect here).

Side-effects and cautions • Heart failure,
• constipation,
• hypotension,
• bradycardia, flushing • Hypotension,
• bradycardia,
• heart failure,
• ankle swelling • Flushing,
• headache,
• ankle swelling

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Centrally acting antihypertensives

Methyldopa not utilised in a patient with abnormal LFTs Examples of centrally acting antihypertensives include: • methyldopa: used in the management of hypertension during pregnancy • moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure • clonidine: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre

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Bosentan • Bosentan is a competitive antagonist of both endothelin-A (ETa) and endothelin-B (ETb) receptors, leading to falls in both pulmonary and systemic vascular resistances without an increase in heart rate • effective in patients with pulmonary arterial hypertension • It is excreted in bile following metabolism by the cytochrome P450 enzymes and this is a potential source of interaction with drugs metabolised by the same isoenzyme
• Common unwanted effects include flushing hypotension dyspepsia
 fatigue Haemoglobin concentrations can fall by up to 1 g/dl during bosentan treatment Hepatotoxicity: The most serious unwanted effect is dose-dependent hepatotoxicity, and it is therefore contraindicated in patients with moderate to severe liver disease Generally, hepatotoxicity occurs within the first 3-4 months of treatment
 teratogenic and therefore contraindicated in pregnancy

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Nitroglycerin • Nitroglycerin products are both venous capacitance dilators and coronary and systemic artery dilators • Administration of nitroglycerin results in: dilation of systemic veins decreased myocardial wall tension decreased oxygen demand vasodilation of large and medium-sized coronary arteries increased coronary blood flow to the subendocardium reduced afterload reduced preload increased ventricular compliance • Nitrates may cause haemolytic anaemia

Nicorandil Action • acts through the opening of potassium channels . • Nicorandil is an activator of ATP-dependent potassium channels • Effect relaxation of smooth muscle in veins venodilatation ↓ ventricular filling pressures + dilatation of the coronary arterioles • It relaxes vascular smooth muscle through membrane hyperpolarisation via increased transmembrane potassium conductance and, like nitrates, through an increase in intracellular cyclic guanosine monophosphate (GMP). Indication • now second-line treatment for angina • Use nicorandil for treatment of stable angina only in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists
Side effects • Headache
 The most common unwanted effect (- 35% of patients),
 appears to be dose-dependent
 resolves with continued treatment • Ulcerations
 oral ulceration, flushing and gastrointestinal disturbances (ulceration of the upper and lower gastrointestinal tract and may present with life threatening bleeding) Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess Contraindication • Use with phosphodiesterase inhibitors such as sildenafil is contraindicated since they can potentiate the hypotensive effects of nicorandil

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Digoxin and digoxin toxicity The half-life of digoxin is around 36-48 hours. This results in a delay before steady plasma levels are seen, it may take a week to start its action

• Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.
• As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.
• digoxin is highly water-soluble • Digoxin has a high volume of distribution and long half-life (36-48 h), which means that loading doses are required to allow the drug to reach a steady-state concentration more quickly. If initiated on a maintenance dose (without loading), it will take several days to reach a steady state. • Digoxin is almost exclusively renally cleared; as a result, renal impairment will significantly alter the half-life of this medication.
Mechanism of action • decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter • Increases the force of cardiac muscle contraction due to inhibition of the Na+/K+ATPase pump which is located in the sarcolemmal membrane.
• Also stimulates vagus nerve What is the pharmacokinetic reason that drives the practice of loading with digoxin? Volume of distribution.
• The volume of distribution for Digoxin is very large (510 litres). This means that administered doses are rapidly distributed to body tissues.
• The initial distribution lasts for some 6-8hrs, which drives the typical loading regimen for Digoxin

of two larger doses (500mcg) some 6-12hrs apart.
• Without loading Digoxin typically takes a few days to reach therapeutic effect. Digoxin can worsen hyperkalaemia
• Translocation of potassium from the cells into the extracellular space can occur from digoxin overdose due to its dose-dependent Na-K-ATPase pump inhibition.

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Digoxin toxicity • Plasma concentration alone does not determine whether a patient has developed digoxin toxicity.
• The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l. Samples taken after 6 h will be more accurate in estimating the body's digoxin
• the mechanism of action leading to tachy-arrhythmias in digoxin toxicity Inhibition of the sodium pump Features • generally unwell, lethargy, anorexia,
 The earliest features of digitalis toxicity include: Nausea, vomiting, anorexia. • cholinergic effects : nausea, vomiting, diarrhea • confusion,
• yellow-green vision • arrhythmias (e.g. AV block, bradycardia)
 (Digoxin toxicity can result in any abnormal cardiac rhythm except type-ll second-degree atrioventricular (AV) block) Precipitating factors • classically: hypokalaemia (hyperkalaemia may also worsen digoxin toxicity, although this is very small print) • increasing age • renal failure • myocardial ischaemia • hypomagnesaemia,
• hypercalcaemia,
• hypernatraemia,
• acidosis • hypoalbuminaemia • hypothermia • hypothyroidism • amyloidosis

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• drugs: amiodarone, quinidine, verapamil, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and loop diuretics Bumetanide is a loop diuretic and may cause hypokalaemia as a side effect. The potassium loss caused by bumetanide increases the toxicity of digoxin.

Management Antidote "KLAM" • slowly normalize K+
• Lidocaine • digoxin Antibodies (anti-dig Fab fragments) • Mg2+

Phenytoin may be used as an alternative to lidocaine (both are class IB agents) if immune therapy is unsuccessful or unavailable in the treatment of tachyarrhythmias secondary to digoxin toxicity.

• Treatment of digoxin toxicity should be guided by the patient's signs and symptoms and the specific toxic effects and not necessarily by digoxin levels alone.
• Activated charcoal if presented within 1 h of an overdose The first-line treatment for acute ingestion is repeated dosing of activated charcoal to reduce absorption and interrupt enterohepatic

circulation.
• Binding resins (eg, cholestyramine)
 may bind enterohepatically-recycled digoxin.
 may be more appropriately used for treatment of chronic toxicity in patients with renal insufficiency.
• correct arrhythmias • severe sinus bradycardia (hemodynamically unstable bradyarrhythmic patients) Atropine • ventricular tachycardia responds best to digoxin immune therapy, but phenytoin and lidocaine are useful if immune therapy is ineffective or unavailable. These drugs depress the enhanced ventricular automaticity without significantly slowing AV conduction • Magnesium sulfate, 2 g IV over 5 minutes, has been shown to terminate dysrhythmias in digoxin-toxic patients with and without overt cardiac disease. Magnesium is contraindicated in the setting of bradycardia or AV block and should be used cautiously in patients with renal failure. • Premature ventricular contractions (PVCs), bigeminy, or trigeminy may require only observation unless the patient is hemodynamically unstable, in which case lidocaine may be effective. • Digibind Its brand name of Digoxin immune fab or Digoxin-specific antibody is an antidote for overdose of digoxin Action: bind to the digoxin unable to bind to its action sites is an immunoglobulin fragment that binds with digoxin.
 first-line treatment for significant dysrhythmias from digitalis toxicity
 Indications for digoxin-specific antibodies include: Hemodynamically unstable arrhythmia Tachyarrhythmias with hypotension
 bradycardia with hypotension that do not respond to atropine

treatment. End organ damage digoxin level > 4ng/ml if chronic ingestion digoxin level > 10 ng/ml if acute ingestion (taken 6 h after the last dose) Hyperkalaemia (if not respond to insulin-dextrose infusions): potassium > 5 mEq/L and symptomatic
 SE Serum sickness • If digoxin-specific antibodies not available lidocaine or phenytoin • Digoxin toxicity related ventricular tachycardia: Phenytoin and lidocaine are useful for ventricular tachycardia if immune therapy is ineffective or unavailable Phenytoin is thought to suppress the pro-arrhythmic properties of digoxin without diminishing its inotropic effects. lidocaine is useful for chemical cardioversion of digoxin toxicity related ventricular tachycardia. This is because it can reduce ventricular automaticity without significantly slowing AV conduction.
 Calcium channel blockers are contraindicated because they may increase digoxin levels. Amiodarone is shown to increase digoxin levels and as such can worsen the risk of rhythm disturbance further. VT in digoxin toxicity is resistant to electrical cardioversion, which may actually precipitate VF and asystole. Bretylium is contraindicated in the treatment of digoxin induced arrhythmias as it can actually precipitate ventricular tachycardia. Quinidine worsens AV and SA conductivity and reduces digoxin tissue binding and is therefore also contraindicated. • conventional dialysis is ineffective • monitor potassium Electrolytes In acute toxicity, hyperkalemia is common Although calcium is often used to ameliorate cardiac toxicity from hyperkalemia, it is not recommended in patients with digoxin toxicity because it can delay after-depolarization and may precipitate ventricular tachycardia or fibrillation. This is based on the fact that intracellular calcium levels are already high in this setting.
 potassium level > 5 mEq/L digoxin Fab fragments Chronic toxicity is often accompanied by

hypokalemia and hypomagnesemia Concomitant hypomagnesemia may result in refractory hypokalemia Correction of electrolyte imbalances may reverse dysrhythmias.

Which measurement would be most useful when monitoring patient for digoxin efficacy? Pulse rate Measuring drug plasma concentration will tell you whether digoxin is at therapeutic concentrations in the blood, but not whether it is having a therapeutic effect.

Chapter 13

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Diuretics Class
Compound
Action
Side effects
Loop Diuretics Furosemide
Bumetanide ethacrynic acid
Thiazides hydrochlorothiazide, indapamide K+ sparing agents spironolactone Aldosterone receptor antagonist
Hyperkalemia

amiloride, triamterene Osmotic Diuretics mannitol Inhibit water reabsorption throughout the tubules, but mostly in the proximal tubule

Loop diuretics Action • Furosemide and bumetanide are loop diuretics that act by inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl.
• There are two variants of NKCC; loop diuretics act on NKCC2, which is more prevalent in the kidneys. Indications • heart failure: both acute (usually intravenously) and chronic (usually orally) • resistant hypertension, particularly in patients with renal impairment Adverse effects • hypotension • hypocalcaemia • hyponatraemia • renal impairment (from dehydration + direct toxic effect) • hypokalaemia • hypochloraemic alkalosis • hyperglycaemia (less common than with thiazides) • ototoxicity • gout

• Loop diuretics induces ototoxicity by affecting Na+/K+/2Cl- cotransporters present in the inner ear.
• Explanation of respond to i.v furosemide but not oral in heart failure Increased bioavailability In right heart failure The patient has a lot of gut oedema which would reduce the absorption of oral furosemide. Intravenous furosemide would have a much better bioavailability and thus therapeutic effect. Protein binding of drugs may be reduced in elderly patients, this may be due to malnutrition.
• Explanation of not responding to furosemide in chronic kidney disease (CKD) Tubular secretion of furosemide is reduced in CKD Organic acids accumulate in renal failure and compete for tubular secretion with furosemide. This competition can be overcome by using a larger dose of the drug. Notes & Notes for MRCP
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inhibit NKCC2 in the thick ascending loop of Henle

Deafness
inhibit NaCl co-transporter in early distal tubule hyponatraemia,
hypokalaemia,
hypercalcaemia

inhibit Na channel in late distal tubule Hyperkalemia

Pulmonary edema

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

A 76-year-old lady taking perindopril 2 mg, bisoprolol 1.25 mg and had recently had her dose of furosemide increased from 40 mg to 80 mg. C/O dizziness, particularly when standing upright after being seated. There were no clinical signs of cardiac failure. Serum urea: 13.3 mmol/L. Serum creatinine: 221 µmol/L. What is the next step in her management?
 Stop the furosemide temporarily and restart at a lower dose within a few days This lady is developing postural hypotension after the recent increase in furosemide dose. She has moderate renal impairment. Stopping either her beta-blocker or ACE inhibitor is not the best option for treatment at this stage.

Bendroflumethiazide

the target of action of thiazide diuretics NaCl co-transporter the target of action of loop diuretics NKCC2 • Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT). • The NaCl co-transporter: the target of thiazide diuretics
 it contributes to the reabsorption of about 10% of the filtered load of sodium.
 Mutations causing loss of function of the NaCl co-transporter cause Gitelman's syndrome, the commonest monogenic cause of hypokalaemia in adults. • Potassium is lost as a result of more sodium reaching the collecting ducts.
• Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload. • The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Bendroflumethiazide - mechanism of Hypokalemia: • ↑ sodium reaching the collecting ducts • Activation of the renin-angiotensin-aldosterone

Which loop diuretic is known to cause sulfa-drug allergy?
 Furosemide Which loop diuretic is used for diuresis in patients allergic to sulfa drugs?
Ethacrynic Acid

Pharmacology

Common adverse effects
• dehydration • postural hypotension • hyponatraemia, hypokalaemia, Hypomagnesaemia, hypercalcaemia • gout • impaired glucose tolerance • impotence Rare adverse effects • thrombocytopaenia • agranulocytosis • photosensitivity rash • pancreatitis • hypochloraemic alkalosis

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Amiloride
• The potassium-sparing diuretic amiloride inhibits sodium channels in the distal segment of the distal convoluted tubule • Amiloride inhibits the action of aldosterone on the distal convoluted tubule producing potassium reabsorption. • In treating a patient with congestive heart failure who develops hypokalaemia, the best choice is to add a small dose of amiloride to his furosemide therapy

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Triamterene
• Triamterene, a potassium sparing diuretic similar to amiloride. • occasionally prescribed with thiazide or loop diuretics, to prevent hypokalaemia.
• It inhibits the movement of sodium through channels towards the end of the distal tubule and collecting ducts, preventing the passage of sodium from the urinary space into the tubular cells. This action causes hyperpolarisation of the apical plasma membrane, preventing the secretion of potassium into the collecting ducts.
• Hyperkalaemia is common (>5%), and is unaffected by concurrent potassium depleting diuretics.
• In mild hyperkalaemia, (eg: K = 5.9 mmol/l) with no evidence of cardiac toxicity. The management involves stopping the triamterene, and repeating the U&E in one week.

Spironolactone • Spironolactone is an aldosterone antagonist
• acts in the cortical distal convoluted tubule and collecting duct. Indications • ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used • hypertension: used in some patients as a NICE 'step 4' treatment • heart failure (see RALES study below) • nephrotic syndrome • Conn's syndrome • Spironolactone is a diuretic with anti-androgen effects. This makes it a useful agent in the treatment of hormonal acne and hirsutism. It blocks the androgen receptor and 5α-reductase enzyme that is responsible for the synthesis of dihydrotestosterone (DHT) and can be used to treat hirsutism. Adverse effects • hyperkalaemia • gynaecomastia Spironolactone and eplerenone are both aldosterone receptor antagonists that have shown survival benefit in patients with NYHA III/IV systolic heart failure.

 Eplerenone has a lower antiandrogenic effect compared to spironolactone and may, therefore, be preferable if patient develops erectile dysfunction and bilateral gynecomastia. RALES • NYHA III + IV, patients already taking ACE inhibitor • low dose spironolactone reduces all-cause mortality

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Eplerenone Indications • Eplerenone is a spironolactone-like agent indicated as an add-on to standard therapy after a myocardial infarction, and heart failure Side-effects • Common side-effects: hyperkalaemia, dizziness, hypotension, diarrhoea, nausea and prerenal renal dysfunction • Uncommon side-effects : eosinophilia, dehydration, hypercholesterolemia and hypertriglyceridaemia Cautions • The drug is metabolised via the CYP3A4 system, so that inducers or inhibitors of the 3A4 enzyme subtype may precipitate drug interactions

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Diuretic abuse • Diuretic abuse is not uncommon amongst athletes and jockeys as a means of weight loss. • The patient has a hypokalaemic alkalosis, and urine potassium excretion is high despite the hypokalaemia.

Respiratory drugs

_____Theophylline • Theophylline, like caffeine, is one of the naturally occurring methylxanthines.
• The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD Action • The exact mechanism of action has yet to be discovered.
• One theory suggests theophyllines may be a non-specific inhibitor of phosphodiesterase resulting in an increase in cAMP.
• antagonism of adenosine and prostaglandin inhibition It blocks the adenosine receptor Blockade of the receptors by theophylline results in: relaxation of smooth muscles, especially bronchial muscles constriction of cerebral blood vessels stimulation of the cardiac pacemaker stimulation of gastric secretions • Theophylline also releases calcium ions from the sarcoplasmic reticulum in skeletal and cardiac muscle, thus enhancing their contractility, including diaphragmatic contractility • plasma theophylline concentration of between 10 and 20 mg/l is required for satisfactory bronchodilatation. Side effect • At therapeutic doses, the side-effect of Aminophylline Jitteriness

• adverse effects can occur within the range 10-20 mg/l and both the frequency
• severity increase at concentrations above 20 mg/l Factors increasing the plasma theophylline concentration: • heart failure • cirrhosis • viral infections • increased age (the elderly) • Diet: Obesity High carbohydrate intake High methylxanthine intake (for example, tea, coffee) • drugs that inhibit its metabolism
 Commonly prescribed drugs that can increase serum theophylline levels include:

clarithromycin, erythromycin
 ciprofloxacin,
 cimetidine,
 oral contraceptives allopurinol.
 Fluvoxamine Consideration should be given to reducing theophylline dose when these drugs are prescribed. • cessation of enzyme-inducing drugs. Factors decreasing the plasma theophylline concentration: (increasing theophylline clearance): • Diet: Low carbohydrate High protein intake • Social: chronic alcoholism without cirrhosis smoking Smoking cessation sudden increase in theophylline level Regular tobacco use up-regulates hepatic enzyme activity; cessation will be associated with a decrease of hepatic enzyme activity, such that theophylline concentrations may increase. • Drugs: drugs that induce liver metabolism: eg:
 Rifampicin Carbamazepine.

Theophylline poisoning • Theophylline has a narrow therapeutic window and needs close monitoring of its serum level to avoid toxicity • Symptoms of toxicity may be delayed following the ingestion of sustained-release preparations for up to 48 h • Theophylline toxicity occurs with concomitant use of clarithromycin due to inhibition of cytochrome P450 (CYP1A2 and CYP3A4) by clarithromycin. • Features of mild to moderate theophylline toxicity include nausea, vomiting, epigastric, tremor, tachycardia, restlessness and hallucinations. Severe toxicity can cause convulsions, arrhythmias and metabolic acidosis. • Studies have shown an approximate 20% increase in both peak and trough theophylline levels with concomitant use of clarithromycin and it is recommended that theophylline levels should be monitored prior, during and on cessation of clarithromycin and dosage

adjustment of theophylline made accordingly. • Features mild to moderate theophylline toxicity nausea, vomiting, epigastric, tremor, tachycardia, restlessness and hallucinations. Severe toxicity: convulsions, arrhythmias metabolic acidosis, hypokalaemia and hyperglycaemia • Management activated charcoal charcoal haemoperfusion is preferable to haemodialysis In cases of severe theophylline toxicity, charcoal haemoperfusion can be used

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Antimuscarinic agent • Muscarinic antagonists (antimuscarinic agents) are a group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors. • Which organ systems are most affected by an antimuscarinic agent depends on the specific characteristics of the agent, particularly its lipophilicity. Lipophilic agents (i.e., atropine or benztropine) are able to cross the bloodbrain barrier and therefore affect the central nervous system (CNS) in addition to other organ systems. Less lipophilic agents (i.e., ipratropium or butylscopolamine) are administered if the CNS does not need to be targeted, specifically for respiratory (e.g., asthma), gastrointestinal (e.g., irritable bowel syndrome), or genitourinary applications (e.g., urinary incontinence).

Pharmacology

Action • Muscarinic antagonists (the majority of anticholinergic drugs) inhibit the effect of acetylcholine on muscarinic receptors, Effects of muscarinic antagonists Muscarinic receptors Organ/Tissue Effects M1, M4, M5 Central nervous system • Influences neurologic function (e.g., cognitive impairment) M2 Heart • ↑ Heart rate • Increases AV-node conduction → arrhythmias M3 Smooth muscle • Gastrointestinal tract ↓ Intestinal peristalsis , ↓ Salivary and gastric secretions • Urinary tract ↓ Bladder contraction (decreases detrusor muscle tone, increases the internal urethral sphincter tone) • Airway Bronchodilation ↓ Bronchial secretions • Eye Mydriasis → narrowing of the iridocorneal angle Impaired accommodation • Blood vessels: minimal effect on vascular tone and blood pressure Exocrine glands • ↓ Secretions (sweat) Antimuscarinic side effects "Blind as a bat (mydriasis), mad as a hatter (delirium), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (decreased secretions and dry skin), the bowel and bladder lose their tone (urinary retention and paralytic ileus), and the heart runs alone (tachycardia).”

Side effect Contraindications Impaired secretion by exocrine glands • Dry mouth and sore throat • ↓ Respiratory tract secretions • Hyperthermia und warm, dry skin Cardiovascular system • Tachycardia • Tachyarrhythmias Decreased smooth muscle tone • Gastroesophageal reflux • Obstipation or ileus • Impaired micturition/urinary retention • Vasodilatation and flush Eye • Mydriasis and photophobia • Blurred vision CNS • Excitement, agitation, and hallucinations with the use of lipophilic parasympatholytics (e.g., atropi ne), especially in elderly patients • Confusion, disorientation • Coma, seizure, and rarely death Notes & Notes for MRCP
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• Acute asthma • Respiratory distress • Heart failure • Myocardial infarction • Hyperthyroidism • Hiatal hernia associated with reflux esophagitis • Ulcerative colitis • Paralytic ileus • Obstructive disease of the gastrointestinal tract (e.g., achalasia, pylori c stenosis or duodenal stenosis) • Obstructive uropathy (e.g., benign prostatic hyperplasia, urinary retention) • Narrowangle glaucoma • Myasthenia gravis

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