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Chapter 13

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

• The bioavailability of an intravenously administered drug is 100% and does not change in renal failure

What is the reason for phenytoin toxicity in patient with chronic renal failure?
 Decreased protein binding of phenytoin
 In CRF, drugs lose some of their affinity for protein binding →↑↑ availability of free drug at any given dose → toxicity
 Because laboratory assays for phenytoin usually measure total drug concentration, this give a false re-assurance (drug level may be within therapeutic range)
 In CRF dose reduction of phenytoin is therefore required
 Other drugs may cause same problem → sodium valporate and warfarin

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First-pass metabolism • This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism.
 As a consequence much larger doses are need orally than if given by other routes.
• This effect is seen in many drugs, including: Aspirin isosorbide dinitrate glyceryl trinitrate lignocaine propranolol verapamil isoprenaline testosterone hydrocortisone morphine • Drugs with high first-pass metabolism should be used with caution in liver disease, since poor hepatic function may lead to their accumulation because of increased bioavailability What is the reason for a different dose of sublingual glyceryl trinitrate (GTN) and oral isosorbide mononitrate? First-pass metabolism

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Drug kinetics (first order + zero order kinetics) • In drugs which have saturation kinetics → initially Small doses of the drug lead to a linear increase in serum drug concentration(follow a linear line) → first order kinetics • Then their metabolism slows down leading to a plateau of the line, for example due to enzyme depletion. Small doses in the drug then lead to large increases in plasma concentration → zero order kinetics.
• Types of drug kinetics
 Zero order kinetics:
 The rate of metabolism and/or elimination remains constant and is independent of the plasma

concentration of a drug at steady state (Cp decreases linearly over time) Zero-order is a capacity-limited elimination. Examples include
 ethanol phenytoin aspirin (at high concentrations)
 heparin
 First order kinetics:
 The rate of metabolism and/or elimination is directly proportional to the plasma concentration of the drug (Cp decreases exponentially over time) First-order is a flow-dependent elimination. Applies to most drugs

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Zero-order kinetics

• Zero-order kinetics describes: metabolic pathways becoming saturated resulting in constant amount of drug being eliminated per unit time (metabolism which is independent of the concentration of the reactant).
• This explains why people may fail a breathalyser test in the morning if they have been drinking the night before • Drugs following zero order kinetics continue to be metabolised at a steady rate, independent of the concentration of the substrate.
• The plot of metabolism against time is linear.

Drugs exhibiting zero-order kinetics Phenytoin Salicylates (e.g. high-dose aspirin) Heparin Ethanol

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Acetylator status • 50% of the UK population are deficient in hepatic N-acetyltransferase • Greater than 60% of Japanese are recognised to be fast acetylators • Approximately 50% of black and Caucasian people are 'slow acetylators' and the rest are 'rapid acetylators'.
• The majority of Eskimos and Orientals are 'rapid acetylators'. • Slow acetylation → ↑↑drug concentrations → ↑↑toxicity from drugs adverse effects.
• Fast acetylation: ↓↓response to the drug effect ↑↑ blood levels of the toxic metabolite
Drugs affected by acetylator status (slow acetylators → increased unwanted effects)

1. isoniazid
    Slow acetylation →↑↑drug concentrations → (peripheral neuropathy and toxic hepatitis
2. hydralazine → drug-induced lupus
3. dapsone → haemolysis and neuropathy but not fibrosis
4. sulfasalazine → haemolysis
5. procainamide

Half-life ↑↑ lipid solubility □ ↑↑tissue binding of the drug □ ↓↓ renal and hepatic clearance rate □ ↑↑ half life

• The half-life is the time taken for the concentration of a drug to reduce by 50% • Plasma half-life is the most important pharmacokinetic factor in determining the appropriate timing between doses • The half-lives are related to:

1. lipid solubility (amiodarone, fluoxetine and diazepam are very lipid-soluble)
2. the rate of drug clearance

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• Steady state: Drug concentration stays constant because the rate of drug elimination equals the rate of drug administration • It takes 1 half-life to reach 50% of the steady-state level, 2 half-lives to reach 25%, 3 halflives to reach 12.5%, and 4 half-lives to reach 6.25%. • Complete steady-state attainment takes 4–5 half-lives for drugs infused at a constant rate; 90% of steady-state level is reached after 3.3 half-lives • Amiodarone the longest half-life = 25 days , fluoxetine 53 h; diazepam 43 h; gentamicin 2-3 h; and bumetanide 0.8 h After 4 half-lives, more than 90% of the drug is eliminated

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Trough level • The lowest concentration reached by a drug before the next dose is administered, often used in therapeutic drug monitoring. • Half-life is the major determinant of trough concentration. • A peak is the highest level of a medication in the blood, while a trough level indicates the lowest concentration.

Affinity & efficacy Drug affinity • a measure of the tendency of a drug to bind to its receptor Drug efficacy • the maximum degree to which a drug activates receptors after binding and triggers a cell response Potency • The potency of a drug is measured as the concentration required to produce a pharmacological response of a specified intensity. • Not related to efficacy (drugs with a high potency can have a low efficacy) but dependent on affinity Therapeutic index • a measurement of the safety of a drug • The greater the therapeutic index, the safer the drug • Drugs with a narrow therapeutic index require monitoring (e.g., lithium, theophylline, warfarin, digoxin, and antiepileptic drugs).

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Dosage intervals Loading dose Why is a loading dose used in amiodarone? Because Amiodarone is widely bound in body tissues • Definition: the amount of an initial dose of a certain drug needed to reach a target plasma concentration • Formula: loading dose = (Cp x Vd) / F □ Cp = target peak plasma concentration at steady state (mg/L or units/L) □ Vd = volume of distribution (L/kg) □ F =

bioavailability • In patients with renal and/or liver dysfunction, loading dose (which does not depend on drug clearance) and time to steady-state are usually unaffected. • Tissue-binding sites must be ‘filled up' by a loading dose before a therapeutic plasma concentration can be achieved. • Metabolism/elimination/clearance rates and plasma half-life determine the time taken to achieve a steady-state plasma concentration and the level of that steady-state concentration when a steady dosing regimen is established. • The loading dose is mainly dependent on the volume of distribution of a drug but in patient with moderate renal failure it depends on renal clearance. • Volume of distribution becomes important particularly when body weight is 40 kg or less. • What is the main factor that determines the choice of loading dose of digoxin in patient with high creatinine? Renal clearance Digoxin is cleared by the kidneys, so the maintenance dose would require adjustment in renal failure. In digoxin both the initial loading dose and the maintenance dose must be reduced in patients with underlying renal disease. • Most useful for drugs which have a long half-life such as: Amiodarone Digoxin Teicoplanin antibiotic inhibit bacterial cell wall synthesis. spectrum of activity similar to vancomycin against Gram-positive bacteria including Staphylococci and Clostridium spp. Oral teicoplanin is effective in the treatment of pseudomembranous colitis Voriconazole Procainamide Fulvestrant (selective estrogen receptor degrader (SERD). used to treat hormone receptor (HR)-positive metastatic breast cancer) Renal or liver conditions lower the maintenance dose without affecting the loading dose.

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Maintenance dose • Definition: The amount of a certain drug needed to achieve a steady target plasma concentration. • Formula: maintenance dose = (Cp x Cl * τ) / F Cp = target plasma concentration at steady state (mg/L) Cl = clearance (L/h) τ = dosing interval (hours) F = bioavailability • In patients with renal and/or liver dysfunction, maintenance dose is decreased (because of impaired drug clearance) and time to steady-state is unchanged (time to steady state depends on t½). Loading dose vs maintenance dose: • Loading doses usually do not need to be adjusted in patients with chronic kidney disease, but maintenance doses should be adjusted by: dose reduction, lengthening the dosing interval, or both. • in renal or liver disease, dosage of the same drug when given as maintenance dose is decreased and when it is given as loading dose is usually unchanged.

Clinical trial: phases Clinical trials are commonly classified into 4 phases; Phase Goal Notes I Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies Conducted on healthy volunteers II Assess efficacy + dosage Involves small number of patients affected by particular disease May be subdivided into: • IIa - assesses optimal dosing • IIb - assesses efficacy III Assess effectiveness Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments IV Postmarketing surveillance Monitors for long-term effectiveness and sideeffects

How many patients would need to be recruited to detect one adverse event? • Roughly speaking, to detect one adverse event in a clinical trial you would need to enrol three times as many patients as the expected event frequency • So If the frequency expected was 1 in 10 000, then you would need to recruit 30 000 patients

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The main factor influencing the time to steady-state is Half-life (t½), not dose or administration frequency.

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Prodrugs Definition • A drug that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; (a precursor of a drug).

Prodrug Active form Note Levodopa Dopamine converted by dopa decarboxylase to dopamine in the brain (in the striatum). Enalapril Enalaprilat S-methyldopa Alpha methylnorepinephrine It is converted to αmethylnorepinephrine by dopamine betahydroxylase →activation of α2 adrenergic receptors in the brainstem → ↓sympathetic output →↓ BP. Loratadine desloratadine non-sedating antihistamine Terfenadine fexofenadine • non-sedating antihistamine • Terfenadine, withdrawn from the market because of serious side effect. • fexofenadine, is safe, does not carry the same risks as the parent compound. salicin salicylic acid salicin is a β-D-glucopyranoside that is cleaved by esterases to release salicylic acid. codeine and morphine (morphineglucuronides) codeine and morphine is enzymatically activated to form sugar derivatives (morphine-glucuronides) that are more active than the parent compound Mercaptopurine Methymercaptopurine ribonucleotide Fluouracil Fluororidine monophosphate Cyclophosphamide Aldophosphamide, Phosphormide mustard Sulfasalazine 5-Aminosalicyclic acid Becampicillin Ampicillin Prednisone Prednisolone Proguanil Proguanil triazine Antimalarial is an inhibitor of dihydrofolate reductase Hydrazide MAO inhibitors Hydrazine derivatives Dipivefrine Epinephrine used to treat open-angle glaucoma

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P450 enzyme system 3 "O" antibiotics inhibitOrs isOniazid , ciprOfloxacine , erythrOmycin 1 "C " antibiotic induCer rifampiCine Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly Inhibitors of the P450 system include

• antibiotics: ciprofloxacin, erythromycin • isoniazid
• cimetidine, omeprazole • amiodarone • allopurinol • imidazoles: ketoconazole, fluconazole • SSRIs: fluoxetine, sertraline
• sulphonamides • Disulfiram
• ritonavir • sodium valproate • acute alcohol intake • quinupristin

Inducers of the P450 system include: • antiepileptics: phenytoin, carbamazepine • barbiturates: phenobarbitone • rifampicin • St John's Wort • chronic alcohol intake • griseofulvin • smoking (affects CYP1A2, reason why smokers require more aminophylline)

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto- induction

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P450 drug interactions: more detail the most important and common reason for drug interactions is the P450 CYP3A4 system. The table below shows the main enzyme systems that are affected by common drugs.

P450 system Substrates Inhibitors Inducers CYP3A4 Macrolides Antiretrovirals Calcium channel blockers simvastatin Macrolides Protease inhibitors (including ritonavir) Imidazoles grapefruit juice CYP2D6 Tricyclic antidepressants Antipsychotics SSRIs Ritonavir CYP2C9 Warfarin Sulfonylureas Imidazoles Amiodarone
Sodium valproate CYP1A2 Theophylline Ciprofloxacin Smoking Omeprazole CYP2E1 Alcohol

Chronic alcohol Isoniazid

Interestingly, codeine and dihydrocodeine are metabolised by cytochrome P450 2D6 to morphine, which provides the analgesic effect; therefore, those patients who are CYP-2D6 poor metabolisers will have a reduced analgesic effect with codeine or Dihydrocodeine

CYP-2C8 CYP-2C18/19 CYP-2D6 Omeprazole Diazepam Tricyclic antidepressants Diazepam Tricyclic antidepressants β-blockers Barbiturates Omeprazole Dihydrocodeine

Proguanil Ecstasy (MDMA)

Selective serotonin reuptake inhibitors

Drug interactions with cytochrome P450 • Drug interactions with the cytochrome P450 system are only clinically significant for drugs that have a narrow therapeutic index (ie small changes in plasma concentrations lead to the drug concentration being either sub-therapeutic or toxic) • Examples of these drugs include: Ciclosporin
 warfarin
 theophylline and phenytoin • Lithium has a narrow therapeutic index owing to changes in absorption and excretion and does not interact with cytochrome P450 Notes & Notes for MRCP
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Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort

Rifampicin

Drugs required therapeutic monitoring

Antiepileptics Antiarrhythmics • Carbamazepine • Phenobarbital • Phenytoin • Valproic Acid

• Digitoxin • Digoxin • Lidocaine • NAPA • Procainamide

Immunosuppressants Antimanics • Cyclosporine • Mycophenolic Acid • Sirolimus • Tacrolimus • Lithium

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Drug induced manifestations

Drug causes gingival hyperplasia

Drug causes of gingival hyperplasia • phenytoin • Ciclosporin • calcium channel blockers (especially nifedipine) Other causes of gingival hyperplasia include • acute myeloid leukaemia (myelomonocytic and monocytic types)

Drugs causing photosensitivity • thiazides • tetracyclines, sulphonamides, ciprofloxacin • amiodarone • NSAIDs e.g. piroxicam • psoralens • sulphonylureas

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Drugs causing specific skin reactions • Psoriatic-type reactions are most commonly caused by beta-blockers
• Antibiotics may cause lupus-type reactions, erythema multiforme, Stevens–Johnson syndrome and erythroderma
• Warfarin is associated with alopecia, as are cytotoxic agents and antithyroid agents
• Phenytoin may cause both acne and gingival hyperplasia

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Antibiotics • Gentamicin • Tobramycin • Vancomycin

Bronchodilators • Theophylline

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Drug affects folic acid metabolism Drugs which inhibit dihydrofolate reductase are: • Methotrexate • Pyrimethamine, and • Trimethoprim. Drugs which interfere with absorption/storage of folate are: • Phenytoin • Primidone, and • Oral contraceptives.

Drug causes SIADH most commonly causes SIADH Other causes • Thiazide diuretics • Vincristine • Vinblastine • Cyclophosphamide • Chlorpropamide • Carbamazepine • Phenothiazines • Tricyclic antidepressants • Clofibrate • Oxytocin • Vasopressin • Morphine • Barbiturates • Nicotine

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Drug causes of urticaria The following drugs commonly cause urticaria: • aspirin • penicillins • NSAIDs • opiates

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Drugs induced galactorrhoea Drug causes of raised prolactin • metoclopramide, Domperidone Domperidone is a dopamine antagonist producing large rises in prolactin concentrations. • phenothiazines • haloperidol • Cimetidine produces hyperprolactinaemia only when given intravenously (IV). • very rare: SSRIs, opioids

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Drugs associated with gynaecomastia • Spironolactone (the most common), causes gynaecomastia by several mechanisms.
 block androgen production by inhibiting enzymes in the testosterone synthetic pathway,
 block receptor binding of testosterone and dihydrotestosterone. increases free oestrogen levels by displace oestradiol from sex hormone binding globulin (SHBG)

Other causes • inhibitors of testosterone synthesis: ketoconazole metronidazole cimetidine, Omeprazole etomidate, and cisplatin. • Oestrogens:
 Digoxin → direct action at oestrogen receptors. • LHRH analogues • Finasteride.

Drug-induced impaired glucose tolerance • Drugs which are known to cause impaired glucose tolerance include: thiazides, furosemide (less common) steroids tacrolimus, ciclosporin interferon-alpha nicotinic acid atypical antipsychotics e.g. olanzapine • Beta-blockers an glycemic status: beta -2-adrenergic antagonism inhibition of hepatic gluconeogenesis
 unselective beta-blockade associated with hypoglycemia (e.g. propranolol rather than the use of beta-1 selective blockers e.g. atenolol, metoprolol). selective beta-1 blockers would not lead to hypoglycaemia - however "...in patients with abnormal energy requirements or metabolism, administration of beta 1-selective-adrenergic antagonists may be associated with hypoglycaemia
 Beta-blockers cause a slight impairment of glucose tolerance.
 They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

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Drug-induced lupus erythematosus The most commonly associated drugs • procainamide
• hydralazine 2,
• anti-TNF alpha agents,
• statins • isoniazid • minocycline.

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• marijuana • heroin • isoniazid • Ciclosporin • calcium-channel blockers • ACE inhibitors • tricyclic antidepressants • busulphan • diazepam

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Drug-induced Pancytopaenia

Drug causes of Pancytopaenia • cytotoxics • antibiotics: trimethoprim, chloramphenicol • anti-rheumatoid: gold, penicillamine • carbimazole (causes both agranulocytosis and pancytopaenia) • anti-epileptics: carbamazepine • sulphonylureas: tolbutamide • Although both azathioprine and mesalazine cause pancytopenia, it is more commonly seen in patients undergoing azathioprine therapy.

Drug-induced thrombocytopenia Drug-induced thrombocytopenia (probable immune mediated) • quinine • abciximab • NSAIDS • diuretics: furosemide • antibiotics: penicillins, sulphonamides, rifampicin • anticonvulsants: carbamazepine, valproate • heparin

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Sulfa drugs • Hypersensitivity reactions to sulfa medications are common and are usually limited to pruritic rashes.
• An acronym for remembering sulfa drugs is Popular FACTSSS: Probenecid,
 Furosemide,
 Acetazolamide, Celecoxib,
 Thiazides,
 Sulfonamide antibiotics,
 Sulfasalazine,
 Sulfonylureas. • Furosemide Most loop diuretic, such as furosemide are sulfa-containing drugs,
 sulfa-containing drugs can cause interstitial nephritis.
 Interstitium is the site of furosemide toxicity.
 For these patients, ethacrynic acid can be used instead, because it does not contain a sulfa group.

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Disulfiram Action • Alcohol antagonist drug used to treat chronic alcoholism
• Ethanol is metabolized by two enzymes:

1. Alcohol dehydrogenase, which is located in the cytosol, converts ethanol to acetaldehyde.
2. Aldehyde dehydrogenase, which is located in the mitochondria , converts acetaldehyde to acetyl CoA. Both enzymes require NAD+ for function.
   • Disulfiram is an inhibitor of aldehyde dehydrogenase and causes accumulation of acetaldehyde, leading to severe nausea and vomiting if alcohol is consumed. Disulfiram reaction
   • The elevations in serum acetaldehyde levels cause the symptoms of disulfiram reaction which include: flushing,

- headache,
- nausea, vomiting
- sweating
- blurred vision,
- dyspnea,
- palpitations, hypotension, chest pain and syncope.

• avoid all alcohol-containing products (e.g., cough and cold syrups, mouthwash, or foods containing alcohol) while taking this medication. • Disulfiram typically causes an acute hepatitis like syndrome 2 to 12 weeks after starting the medication that can be severe and lead to acute liver failure or need for liver transplantation.

Disulfiram inhibitor of Aldehyde dehydrogenase, which is located in the mitochondria
Fomepizole inhibitor of Alcohol dehydrogenase, which is located in the cytosol

The target of disulfiram is located in which cellular compartments?
 Mitochondria

Drug-induced ethanol intolerance (disulfiram-like reaction) • As in the case with disulfiram, the underlying mechanism is believed to be the accumulation of acetaldehyde in the blood, due to inhibition of the hepatic aldehyde dehydrogenases.
• drugs which can produce DISULFIRAM like reaction when taken with Alcohol: chloramphenicol, furazolidone, nitroimidazole antibiotics, including metronidazole, and quinacrine, First-generation sulfonylureas, e.g. tolbutamide and chlorpropamide cephalosporins, including cefoperazone, cefamandole and cefotetan antifungal eg: Griseofulvin Procarbazine

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Drug-induced long QT

Commonly medications that cause QT prolongation class Examples Antiarrhythmic
• Amiodarone
• Disopyramide
• Ibutilide • Procainamide • Quinidine
• Sotalol
antipsychotics • Chlorpromazine
• Clozapine • Haloperidol • Quetiapine • Risperidone
• Thioridazine
antibiotics • Azithromycin • Clarithromycin
• Erythromycin
• Ciprofloxacin • Levofloxacin • Ofloxacin
• Trimethoprim – sulpha • Ketoconazole • Fluconazole • itraconazole Antidepressants • Amitriptyline • Citalopram • Desipramine • Doxepin • fluoxetine • Imipramine • Nortriptyline • Paroxetine • Sertraline • venlavaxine Antiemetics • Ondansetron

• prochlorperazine

Drugs causing ocular problems

Visual disturbance cataract Corneal opacities

Yellowgreen tinge Drug steroids Amiodarone Indomethacin

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

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Optic neuritis

Retinopathy

Blue tinge in vision Sildenafil

Digoxin Ethambutol Amiodarone Metronidazole

Chloroquine, quinine

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Drug induced photosensitivity

Rash on the forearms and face is typical of a photosensitivity rash

• Thiazides • Tetracyclines, sulphonamides, ciprofloxacin • Amiodarone • NSAIDs e.g. Piroxicam • Psoralens • Sulphonylureas Mnemonic: FAST-N (Fluoroquinolones eg: cipro. Amiodarone. Sulfo.Tetracyclines. NSAIDs)

Drug induced ototoxicity • Causes Aminoglycosides Streptomycin → irreversible cochlear and vestibular dysfunction Platinum-based antineoplastic agents,
 Salicylates Quinine
 Loop diuretics. • Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
• The time of onset is unpredictable: marked hearing loss can occur even after a single dose.
 may occur several weeks or months after completion of antibiotic or antineoplastic therapy. • Usually irreversible with most agents.

Drug induced seizures • Drugs that cause seizures as a drug reaction include: Isoniazid (vitamin B6 deficiency) Bupropion,
 Imipenem/cilastatin Tramadol Enflurane

Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane.

With seizures, I BITE my tongue.

Drug causes erythema multiforme, and the Stevens-Johnson syndrome subtype. • Allopurinol → (the Most commonly associated) • Recent drugs - nevirapine, lamotrigine, sertraline, pantoprazole, tramadol • Antibiotics - sulphonamides, co-trimoxazole, penicillin, cephalosporins, fluoroquinolones, vancomycin • NSAIDs - piroxicam, fenbufen, ibuprofen, ketoprofen, naproxen, tenoxicam, diclofenac, sulindac

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• Anti-TB - rifampicin, ethambutol, isoniazid, pyrazinamide • Anticonvulsants - barbiturates, carbamazepine, phenytoin, valproate, lamotrigine • Antifungals - fluconazole, nystatin, griseofulvin • Antidepressants - lamotrigine, sertraline. • Sulfasalazine

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Drugs which act on serotonin receptors • Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system.
• It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis.
Agonists • sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine • ergotamine is a partial agonist of 5-HT1 receptors Antagonists • pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks.
• Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis • cyproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome • ondansetron is a 5-HT3 receptor antagonist and is used as an antiemetic 5HT-2 receptor inhibition
• 5HT-2 receptor inhibition also reduces platelet aggregation • one example is sarpogrelate developed in North East Asia primarily as an alternative to aspirin because of its association with a lower risk of haemorrhage.

Drugs that can be cleared with Hemodialysis - mnemonic: BLAST

• Barbiturate • Lithium • Alcohol (inc methanol, ethylene glycol) • Salicylates • Theophyllines (charcoal
hemoperfusion is preferable) Drugs which cannot be cleared with HD include • Tricyclics • Benzodiazepines (diazepam, midazolam, alprazolam)

• Dextropropoxyphene (co-proxamol) • Digoxin, β-blockers

Cardiovascular drugs

Prescribing in patients with heart failure The following medications may exacerbate heart failure: • thiazolidinediones: pioglitazone is contraindicated as it causes fluid retention pioglitazone is now the only thiazolidinedione on the market
• verapamil: negative inotropic effect • NSAIDs & glucocorticoids: should be used with caution as they cause fluid retention low-dose aspirin is an exception - many patients will have coexistent cardiovascular

disease and the benefits of taking aspirin easily outweigh the risks • class I antiarrhythmics; flecainide (negative inotropic and proarrhythmic effect) • Celecoxib (rofecoxib has been withdrawn) acts by inhibiting prostaglandin synthesis via inhibition of cyclo-oxygenase-2 (COX-2).It causes fluid retention and can worsen an already pre-existing heart failure. The CSM reminds prescribers that celecoxib is contraindicated in: patients with severe congestive heart failure, active peptic ulceration
 or gastrointestinal bleeding.

Antiarrhythmics: Vaughan Williams classification The Vaughan Williams classification of antiarrhythmics is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and magnesium AP = action potential Class Examples Mechanism of action Ia Quinidine Procainamide Disopyramide

1. Block sodium channels
2. Increases AP duration Notes: • Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) • Procainamide may cause drug-induced lupus • Disopyramide toxicity Urinary retention
   Ib Lidocaine Mexiletine Tocainide
3. Block sodium channels
4. Decreases AP duration Ic Flecainide Encainide Propafenone
5. Block sodium channels
6. No effect on AP duration II Propranolol Atenolol Bisoprolol Metoprolol Beta-adrenoceptor antagonists III Amiodarone Sotalol Ibutilide Bretylium Block potassium channels IV Verapamil
   Diltiazem Calcium channel blockers

Antiarrhythmic agents • Calcium-channel blockers act mainly on (SA) (AV) nodes (direct membrane effect), as these structures are almost exclusively depolarised by the slow calcium channels
• Flecainide binds to the sodium channel and decreases the speed of depolarisation (in other words, decreases conduction velocity) (Slows the upstroke of the action potential) • Atenolol decreases sympathetic tone • Amiodarone and sotalol increase the action-potential duration and therefore the refractory periods
 they have little effect on conduction velocity
 Sotalol have a high risk of producing torsades de pointe • Class V agents (digitalis agents) affect SA and AV nodes by increasing vagal tone

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Atropine Action • Atropine is an antagonist of the muscarinic acetylcholine receptor Uses • Treatment of organophosphate poisoning • Bradycardia , heart block
Physiological effects • Tachycardia • Mydriasis • ↓ Secretions of exocrine glands • ↓ Tone and motility of smooth muscles (i.e., ↓ urgency in cystitis) • ↓ Cholinergic overactivity in CNS

MRCPUK-part-1-january 2018 exam: Which physiological effect would be expected following administration of atropine? Tachycardia + mydriasis

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Adenosine

Mechanism of action • causes transient heart block in the AV node • agonist of the A1 receptor which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux • Acts on specific adenosine cell surface receptors (A1 and A2)
• Stress testing: A2A adenosine receptor agonist;
 activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow • ↑ coronary vasodilatation (Adenosine is an important mediator of metabolic vasodilatation)
• Increasing O2 demands are met by adenosine production vasodilatation increased blood supply. • Adenosine effect on renal In the renal vasculature, in contrast, adenosine can produce vasoconstriction However, the vasoconstriction elicited by an intravenous infusion of adenosine is

only short lasting, being replaced within 1-2 min by vasodilatation.
 It appears that the steady-state response to the increase of plasma adenosine levels is global renal vasorelaxation that is the result of A2A receptor activation Adenosine lowers glomerular filtration rate (GFR) by constricting afferent arterioles, especially in superficial nephrons. In contrast, it leads to vasodilation in deep cortex and medulla. • ↓↓ sinus node automaticity and AVN conduction. • adenosine has a very short half-life of about 8-10 seconds • Inactivated by adenosine deaminase.
Adverse effects • transient facial flushing (18%) (most common) • bronchospasm Dyspnea (12%)
 It should be avoided in asthmatics

• choking sensation, where patients often clutch their chest • chest pain • can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome) Interaction
• The effects of adenosine are enhanced by dipyridamole (anti-platelet agent)
 Adenosine transported out of the cell to the extracellular space by specific bidirectional nucleoside transporters. Inhibitors of these transporters, such as dipyridamole, increase the extracellular concentrations of adenosine and are useful clinically to treat certain cardiovascular complications.
• Adenosine effects blocked by theophyllines. • Unlike verapamil it may be used following β-blockade

Adenosine is a coronary vasodilator (which is why we use it in cardiac stress testing) and a bronchoconstrictor (action opposed by theophylline).

Flecainide Action • Flecainide is a Vaughan Williams class 1c antiarrhythmic.
• It slows conduction of the action potential by acting as a potent sodium channel blocker.
 Slows the upstroke of the action potential does not alter the overall length of the action-potential duration. • This may be reflected by widening of the QRS complex and prolongation of the PR interval Indications • atrial fibrillation • SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome Contraindications • post myocardial infarction increase mortality Adverse effects • negatively inotropic • bradycardia • proarrhythmic • oral paraesthesia • visual disturbances

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Amiodarone

• Amiodarone is a class III antiarrhythmic agent
• used in the treatment of atrial, nodal and ventricular tachycardias. • metabolized in the liver via cytochrome P450 3A4.
Action • The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential.
 Amiodarone prolongs the refractory period of the cardiac conducting system. Its antiarrhythmic effects are due mostly to the inhibition of the rapid component of the delayed potassium rectifier IKr channel (as with sotalol) but also have an effect on the slow component.
• Amiodarone also has other actions such as blocking sodium channels (a class I effect) Several factors limit the use of amiodarone:
• long half-life (20-100 days) Because of its long half-life there is a potential for drug interactions to occur for several weeks after amiodarone has been stopped. • should ideally be given into central veins (causes thrombophlebitis) • has proarrhythmic effects due to lengthening of the QT interval • interacts with drugs commonly used concurrently e.g. Decreases metabolism of warfarin
• numerous long-term adverse effects. Monitoring of patients taking amiodarone • TFT, LFT, U&E, CXR prior to treatment • TFT, LFT every 6 months and for up to 12months after discontinuation

of amiodarone An increase of up to 40% above the baseline T4 is a normal effect of amiodarone. This occurs approximately 2 months after initiation of therapy & does not require discontinuation.
Administration
• 300 mg of amiodarone made up to 20 ml with 5% dextrose given as an intravenous bolus is the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular tachycardia (100 mg of lidocaine may be given intravenously when amiodarone is unavailable). Adverse effects
corneal deposits is the most common side effect hypothyroidism occur more frequently than hyperthyroidism

• Thyroid dysfunction: both hypothyroidism and hyperthyroidism
 Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3)→ hypo (occurs in up to 20% of patients taking amiodarone) It is also a potential source of large amounts of inorganic iodine → hyper (occurs in 3% of patients in iodine-deficient areas, but in 20% in areas where iodine is sufficient). • Corneal deposits present in most patients,
 almost universal in patients taking amiodarone therapy (at least 90%).

 rarely interfere with vision, becomes manifest by the presence of night-time visual glare, noticed while driving.
 usually reversible on withdrawal of drug • Photosensitivity Skin deposits result in photodermatitis and a greyish-blue discoloration on sun-exposed areas ('slate-grey' appearance (Skin sensitivity)
 can be prevented by using a sun block
• Pulmonary fibrosis/pneumonitis (5-7%). • Liver cirrhosis/hepatitis • Peripheral neuropathy, myopathy • Prolonged QT interval • Thrombophlebitis and injection site reactions • Bradycardia • Persistent slate-grey skin discoloration (ceruloderma)

 more common in males than females. the pigmentation consists of brownish-yellow deposits of amiodarone, iron and others (not including melanin or hemosiderin)
 On biopsy of these lesions, which cell type is laden with pigment? histiocytes of the dermis
 appears in sun-exposed areas and is thought to be activated by an UVArelated hypersensitivity response.
 Sun exposure is not recommended for patients on amiodarone.
 Treatment discontinuation of the drug
 if not disappeared after discontinuation → laser-based therapy. • Neutropenia • Nightmares, sleep disturbance Important drug interactions of amiodarone • Decreased metabolism of warfarin, therefore increased INR Decrease warfarin dose by 33- 50% and monitor the INR weekly • Increased digoxin levels the dose of digoxin should be halved when patients are started on amiodarone. • There is an increased risk of ventricular arrhythmias when amiodarone is given with tricyclics, hence concomitant use should be avoided.

For amiodarone and the thyroid gland (See Endocrinology chapter)

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Dobutamine & Dopamine Dobutamine Dopamine Action • Direct Sympathomimetics (β1 receptor agonist) • β1> β2, agonist • positive inotropic effect

> chronotropic effects • D1 = D2 > β > α • Chronotropic effects at lower doses (β effect) • Vasoconstriction at high doses (α effect) Indications • Cardiogenic shock • Acute heart failure • Cardiac stress testing • Heart failure • Cardiogenic shock • Unstable bradycardia

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Adrenaline Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties. The β- effect will cause significant tachycardia Indications • anaphylaxis • cardiac arrest Recommend Adult Life Support (ALS) adrenaline doses • anaphylaxis: 0.5ml 1:1,000 IM • cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV Management of accidental injection • local infiltration of phentolamine • An alternative possibility is locally applied GTN paste Anaphylaxis • Where there is a history of a typical allergic reaction, current United Kingdom resuscitation guidelines suggest adrenaline if there is: Stridor Wheeze Respiratory distress, or Clinical evidence of shock. • Adrenalin is used for its alpha-agonist effects that include increased peripheral vascular resistance and reversed peripheral vasodilatation, systemic hypotension, and vascular permeability.

• Beta-agonist effects include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects. • IM administration is preferred because of a superior safety profile with respect to cardiac adverse events compared with the IV route, although 1:10000 adrenalin IV may be used in a life-threatening situation. • The intramuscular (IM) route for adrenaline is the route of choice for most healthcare providers. • Adult EpiPen which allergy sufferers can carry with them contains 0.3 mg or 0.15 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Antiplatelets

Overview of antiplatelet agents

Overview of antiplatelet agents Group Agents Indications Adverse effects Irreversible cyclooxygenase inhibitors Acetylsalicylic acid (aspirin) • Acute coronary syndrome • Ischemic stroke • Primary and secondary prevention of cardiovascular disease excretion P2Y12 receptor antagonists (ADP receptor inhibitors) • Clopidogrel • Prasugrel • Ticagrelor • Ticlopidine • Cangrelor • Dual antiplatelet therapy (with acetylsalicylic acid) in ACS • Alternative to aspirin Glycoprotein IIb/IIIa inhibitors • Abciximab • Eptifibatide • Tirofiban • High-risk patients with unstable angina/NSTEMI before undergoing PCI

• Reye syndrome • Aspirin exacerbated respiratory disease • GI upset • Salicylate toxicity • Affects the kidneys in a dosedependent manner Low doses → uric acid retention High doses → uric acid • Allergic reactions • Haemorrhage • GI upset • Acute thrombocytopenia • Haemorrhage

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Summary of latest guidance The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis 1st line 2nd line NSTEMI Aspirin (lifelong) & clopidogrel (12 months) If aspirin contraindicated, clopidogrel (lifelong) STEMI Aspirin (lifelong) & clopidogrel (1m if no/bare stent, 12 m if drug-eluting stent) If aspirin contraindicated, clopidogrel (lifelong) TIA* Clopidogrel (lifelong) Aspirin (lifelong) & dipyridamole (lifelong) Ischaemic stroke Clopidogrel (lifelong) Aspirin (lifelong) & dipyridamole (lifelong) Peripheral arterial disease Clopidogrel (lifelong) Aspirin (lifelong) *the guidelines for TIA are based on the 2012 Royal College of Physicians National clinical guideline for stroke. These guidelines corrected the anomaly where patients who've had a stroke were given clopidogrel, but those who'd suffered a TIA were given aspirin + dipyridamole.
Peri-Operative Management of Anticoagulation and Antiplatelet Therapy (British society for Haematology guidelines 2016)
• Warfarin and other vitamin K antagonists Emergency surgery in patients on warfarin If surgery can wait for 6–8 h then 5 mg of intravenous phytomenadione can restore coagulation factors;
 if this is not possible, anticoagulation can be reversed with 25–50 u/kg of fourfactor prothrombin complex concentrate Consider bridging with treatment dose heparin in:

1. Patients with a VTE within previous 3 months.
2. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5.
3. Patients with a previous stroke/TIA in last 3 months.
4. Patients with a previous stroke/TIA and three or more of the following risk factors: Congestive cardiac failure Hypertension (>140/90 mmHg or on medication) Age >75 years Diabetes mellitus
5. mechanical heart valve (MHV) patients other than those with a bileaflet aortic valve and no other risk factors the post-operative bridging (i.e. full dose anticoagulation) should not started until at least 48 h after high bleeding risk surgery although thromboprophylaxis should be given if indicated. Warfarin should be stopped for 5 days before an elective procedure if anticoagulation needs to be discontinued • Antiplatelet therapy aspirin monotherapy (for secondary prevention of cardiovascular disease) can be continued for most invasive non-cardiac procedures Aspirin can be continued both before and after coronary artery bypass surgery The lifespan of a platelet is 7–10 days. If aspirin is held prior to surgery, it should be discontinued one week in advance.