High Risk Drugs

Part 2

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Learning Outcomes

By the end of this webinar you will be able to:

- Understand the key high risk drugs listed in the GPhC framework.
- Understand key information associated with high risk drugs, as well as the medical emergencies associated with them and their management.

7. Drugs with a narrow therapeutic index

- Gentamicin
- Warfarin
- Lithium
- Digoxin
- Theophylline
- Methotrexate
- Phenytoin
- Insulin
- Ciclosporin

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What are the reference ranges and the effects on increased plasma concentrations?

Name	Reference ranges	Effects of increased concentrations in plasma
Gentamicin	5 to 10mg/L	Ototoxicity, renal failure
Warfarin	INR 2-3.5 dependent on indication	Bleeding
Lithium	0.4 to 1 mmol/L	Tremor, coma
Digoxin	1 to 2 mcg/L	GI disturbance, arrhythmias, xanthospia
Theophylline	10 to 20mg/L	Arrhythmias, seizures
Methotrexate	Monitor levels of FBC, LFTs	Myelosuppression
Phenytoin	10 to 20mg/L	Arrhythmias, cerebellar syndrome
Ciclosporin	Depends on clinical situation and indication for treatment: IV = 150-250 ng/mL oral = 100-200 ng/mlL	Renal failure

Gentamicin: Monitoring

- Renal function
- Auditory and vestibular function
- Serum-aminoglycoside concentration

Gentamicin: Warning Signs

- Hearing impairment/disturbance

Gentamicin: Actions Needed

- Report immediately if any of the warning signs occur
- Ensure patient is hydrated and drinking adequate amounts of fluid to prevent dehydration before starting treatment

Gentamicin: Interactions

- Increased risk of **nephrotoxicity** when given with ciclosporin, tacrolimus, vancomycin
- Increased risk of **ototoxicity** when given with loop diuretics, vancomycin

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Warfarin: Monitoring

- Check baseline LFTs, FBC and clotting screen (prothrombin time (PT) and INR)
- Monitor patients with increased risk of bleeding
- Monitor patients with increased risk of over-coagulation

Warfarin: Warning Signs

- Haemorrhage
- Risk of calciphylaxis

Warfarin: Actions Needed

- Report immediately if any of the warning signs occur
- Ensure patient has an anticoagulant treatment booklet

Warfarin: Interactions

- Diet, including Vitamin K
- Alcohol
- Medication

Lithium: Monitoring

- Serum lithium concentration
- Renal function (eGFR)
- Cardiac function (ECG)
- Thyroid function (TFTs)
- FBC
- BMI
- Serum electrolytes

Lithium: Warning Signs

- Increasing GI disturbances
- Visual disturbances
- CNS disturbances
- Renal dysfunction
- Incontinence, polyuria
- Fine tremor increasing to coarse tremor, muscle weakness
- In severe overdosage: seizures, coma, renal failure, arrhythmias, blood pressure changes, circulatory failure, sudden death

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Lithium: Actions Needed

- Report immediately if any of the warning signs occur
- Ensure they remain on the same brand of lithium
- Adequate salt and water intake
- Counsel patient

Lithium: Interactions

- NSAIDs
- ACEI/ ARBs
- Metronidazole
- Erythromycin
- Thiazides diuretics
- Steroids
- SSRIs
- Tricyclics
- Amiodarone
- Diltiazem
- Verapamil
- Antidepressants
- Antipsychotics
- Antihistamines
- Antimalarials

Digoxin: Monitoring

- Serum electrolytes (K^+, Mg^{2+}, Ca^{2+})
- Renal function
- Heart rate

Digoxin: Warning Signs

- Cardiac
- Neurological
- Gastrointestinal
- Skin
- Visual

Digoxin: Actions Needed

- Report immediately if any of the warning signs occur
- Dosage forms have different bioavailabilities:
  - Intravenous: 100%
  - Tablet: 50-90%
  - Elixir: 75%

Digoxin: Interactions

- Amiodarone
- Macrolides
- Gentamicin
- Tetracyclines
- Diltiazem
- Verapamil
- IV Calcium salts
- Vitamin D
- Loop and thiazide diuretics
- NSAIDs
- ACE inhibitors
- St. John's Wort

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Theophylline: Monitoring

- Serum potassium
- Plasma theophylline concentration

Theophylline: Warning Signs

- Toxicity
- Symptoms of uncontrolled asthma
- Frequent courses of antibiotics and/or oral corticosteroids

Theophylline: Actions Needed

- Report immediately if any of the warning signs occur
- Inform the patient of potential interactions with theophylline and the need to check with a pharmacist or doctor before taking any new medication
- To inform their GP before stopping or starting smoking
- Maintain the same brand of medicine

Theophylline: Interactions

- β_2 agonists
- Steroids
- Diuretics
- Smoking
- Alcohol
- Caffeine
- Allopurinol
- Diltiazem
- Macrolide
- Oral contraceptives
- Propranolol
- Verapamil
- Quinolones

Methotrexate: Monitoring

- FBC
- Renal function
- Liver function

Methotrexate: Warning Signs

- Blood dyscrasias
- Gastro-intestinal toxicity
- Liver toxicity
- Pulmonary toxicity
- Pregnancy and breast feeding

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Methotrexate: Actions Needed

- Report immediately if any of the warning signs occur
- Counsel on how to take methotrexate and what to avoid
- Methotrexate treatment booklet
- Importance of effective contraception during treatment
- Annual flu vaccine but live vaccines should be avoided

Methotrexate: Interactions

- Penicillins
- Glycopeptides
- Sulfonamides
- Ciprofloxacin
- Phenytoin and Barbiturates
- Oral contraceptives
- Thiazide diuretics
- Oral hypoglycaemics
- Tetracyclines
- NSAIDs
- PPIs
- sulfamethoxazole (co-trimoxazole)
- trimethoprim

Phenytoin: Monitoring

- Serum concentration
- ECG and blood pressure with intravenous use
- LFTs
- FBC
- Serum folate
- Vitamin D

Phenytoin: Warning Signs

- Toxicity
- Skin disorders
- Blood disorders
- Suicidal thoughts
- Low vitamin D levels

Phenytoin: Actions Needed

- Report immediately if any of the warning signs occur
- Brand specific prescribing recommended

Phenytoin: Interactions

- Amiodarone, chloramphenicol, cimetidine, disulfiram, diltiazem, fluconazole, fluoxetine, miconazole, topiramate, trimethoprim, metronidazole, clarithromycin, telithromycin
- Rifamycins, St John's Wort, theophylline, itraconazole, ciclosporin

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Ciclosporin: Monitoring

- FBC
- Serum electrolytes (K^+, Mg^{2+})
- LFTs
- Renal function
- Blood lipids
- Blood pressure
- Dermatological and physical examination

Ciclosporin: Warning Signs

- Nephrotoxicity
- Neurotoxicity
- Blood disorders
- Liver toxicity
- Other signs of toxicity - vomiting, drowsiness, tachycardia
- Hypertension
- Gingivial hyperplasia

Ciclosporin: Actions Needed

- Report immediately if any of the warning signs occur
- Brand specific prescribing recommended
- Regular blood pressure monitoring
- Warn patients that they must not receive immunisation with live vaccines
- Advise patient to avoid excessive exposure to UV light and to use a wide-spectrum sunscreen
- Advise patient to avoid a high potassium diet and grapefruit juice

Ciclosporin: Interactions

- Clarithromycin, diltiazem, erythromycin, fluconazole, grapefruit juice, itraconazole, ketoconazole, miconazole, metoclopramide, verapamil, colchicine and tacrolimus
- Carbamazepine, orlistat, phenobarbital, phenytoin, rifampicin, St. John's Wort

8. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Monitoring:

- Haemoglobin in those with risk factors for GI bleeding
- Blood pressure
- Liver function
- Renal function

Warning Signs

- Black stools or 'coffee ground' vomit
- Iron deficiency anaemia
- Worsening of asthma
- Pregnancy and breastfeeding
- Swollen ankles or feet
- Unexplained, persistent recent-onset dyspepsia

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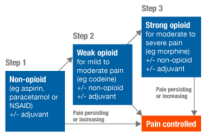
Actions Needed

- Report immediately if any of the warning signs occur
- Check that the NSAID prescribed is suitable for the patient
- Take the lowest effective dose and for shortest period of time to control symptoms
- Check if require co-prescription of gastro-protection
- Oral NSAID should be taken with or just after food
- Ensure patient checks with a pharmacist or doctor before taking any new medication

Interactions

- Quinolones
- Coumarins and phenindione
- Corticosteroids
- Antihypertensives and diuretics
- Cardiac glycosides
- Lithium
- Methotrexate
- Ciclosporin
- Antiplatelets
- SSRIs

10. Opiates



Adjuvant analgesics : drugs with other 1° indications (often neurological) but which are also effective at providing relief from pain. These include some antidepressants, mostly TCAs, and some antiepileptic drugs e.g. carbamazepine and gabapentin (which is specifically useful for neuropathic path)

- **Intractable constipation** (try transdermal fentanyl)
- **Decline in renal function** (try transdermal fentanyl)
- **Opioid-induced hyperalgesia or signs of neurotoxicity** (e.g. cognitive failure, delirium, hallucinations, myoclonus, allodynia). Try oxycodone or methadone

Opioids

- IR morphine can be given for breakthrough pain
- When switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by ¼ - ½
- Increments of morphine should not exceed 1/3 – 1/2 of the total daily dose every 24 hrs

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Opioids

- Oral bioavailability of morphine can be poor
- Morphine (and its metabolites) are renally excreted, it can accumulate in patients with renal failure, resulting in opioid toxicity
- Patients with renal impairment tend to be prescribed alternative products such as transdermal buprenorphine or fentanyl patches

Transdermal Preparation

- Transdermal preparations of fentanyl and buprenorphine are available
- They are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose

Parenteral administration of morphine and diamorphine

When converting oral morphine to:

S/C morphine: The total previous 24-hour requirements of oral morphine are **divided by two** to give the equivalent S/C morphine dose.

S/C diamorphine: The total previous 24-hour requirements of oral morphine should be **divided by three** to give the total 24-hour equivalent dose of parenteral diamorphine.

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Equivalent doses and calculation of breakthrough pain doses

Equivalent S/C diamorphine dose	Equivalent S/C morphine dose
Diamorphine 60mg over 24 hours (corrected to nearest practical dose)	Morphine 100mg over 24 hours (corrected to nearest practical dose)
Breakthrough dose = total 24-hour requirement/6 60mg (of diamorphine)/6 = 10mg diamorphine s/c (prn)	Breakthrough dose = total 24-hour requirement/6 100mg (of morphine)/6 = 15mg morphine s/c (prn)

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