

## CLINICAL PHARMACOLOGY NOTES

**Bioavailability** refers to absorption of the drug. Increased gastric emptying and induction of liver enzymes increases first pass metabolism and reduced bioavailability.

**Potency** refers to the amount of drug usually needed to produce an effect, such as relief of pain or reduction of blood pressure. For instance, if 5 milligrams of drug A relieves pain as effectively as 10 milligrams of drug B, drug A is twice as **potent** as drug B.

**Efficacy** refers to the potential maximum therapeutic response that a drug can produce. Frusemide eliminates more salt than hydrochlorothiazide, hence it has higher **efficacy** than hydrochlorothiazide.

The difference in speed of **acetylation** is due to the amount (or activity) of the enzyme N-acetyltransferase available. **Fast acetylation** is a trait which is autosomal dominant inherited.

### Drugs with zero order kinetics

Alcohol  
Phenytoin  
Fluoxetine

### LIVER ENZYME INDUCERS (PCBRAS)

Phenytoin  
Carbamazepine  
Barbiturates  
Rifampicin  
Alcohol  
Sulphonylureas

### LIVER ENZYME INHIBITORS (OAAK DEVICCES)

Omeprazole  
Amiodarone  
Allopurinol  
Ketoconazole  
Disulfram  
Erythromycin  
Valproate  
Isoniazid  
Ciprofloxacin  
Cimetidine  
Ethanol  
Sulphonamides

**Drug induced lupus:**

procainamide  
isoniazid  
chlorpromazine  
penicillamine  
sulfasalazine  
hydralazine  
methyldopa  
quinidine

Drugs which can cause **gynaecomastia** are :

digoxin  
oestrogens  
spironolactone  
cimetidine  
verapamil  
nifedipine

Drugs causing **galactorrhoea** are:

Oral contraceptive pills  
Phenothiazines such as chlorpromamide and thioridazine  
Metoclopramide  
Bromocriptine

The drugs most commonly implicated in **SIADH** are:

cyclophosphamide  
chlorpromamide  
carbamazepine  
clofibrate  
thiazide diuretics  
vincristine  
vinblastine  
phenothiazines  
tricyclic antidepressants  
SSRIs

Drugs producing **hypercalcemia** include:

lithium,  
alkaline antacids  
DES,  
Thiazides  
estrogens  
progesterone

**MISCELLANEOUS DRUGS**

Common side effects of **Selective Serotonin Reuptake Inhibitors (SSRIs)** are nausea, vomiting, diarrhoea, appetite and weight loss, sexual dysfunction and deranged liver function tests. Similarly, the common side effects of **fluoxetine** are :anxiety or nervousness; decreased appetite; diarrhoea; drowsiness; headache; increased sweating; nausea; tiredness or weakness; trembling or shaking; insomnia.

**Amiodarone** blocks conversion of T4 to T3 and affects pituitary thyroid axis. The following changes in thyroid function tests occur within 3 months of starting amiodarone and are not indicative of thyroid disease:  
increase in TSH up to 20mU/L  
increase in T4 to upper limit of normal  
decreased T3 levels.

**Anticholinergic syndrome** occurs following overdose with drugs that have anticholinergic activity.

Examples of these are tricyclic antidepressants, antihistamines and atropine. Features include flushed skin, urinary retention, tachycardia, mydriasis (dilated pupils) and agitation.

Physostigmine, a reversible inhibitor of acetylcholinesterase, is effective in treating anticholinergic symptoms but there is a significant risk of cardiac toxicity (bradycardia, AV conduction defects and asystole) with the drug.

**Bisphosphonates** acts at the cellular level. They act directly or indirectly on the osteoclasts. The effect can be on the formation of osteoclasts and/or on their activity. A decrease in osteoclast number can occur either through direct action on osteoclast precursors, or indirectly by stimulating the osteoblasts to produce an inhibitor of osteoclast formation. Osteoclast inactivation is associated with bisphosphonate uptake from the bone surface.

**β-interferon** is a long term treatment (as opposed to steroids for acute relapses) which is of benefit only in the *relapsing remitting form* (about 40% of MS patients have this form), and slows progression of disability and reduces demyelinating lesions.

**Aspirin** toxicity causes symptoms of nausea, vomiting, headache, confusion and tinnitus or hearing difficulties.

Major side effects of **carbimazole** are: agranulocytosis, thrombocytopenia, acute hepatic necrosis, cholestatic hepatitis, lupus-like syndrome and vasculitis. It may cause neutropenia in 1 in 800 patients.

**Clozapine induced agranulocytosis** occurs in about 1% to 10% of patient who take clozapine. Patients who have experienced agranulocytosis with prior treatment of clozapine should not receive clozapine again.

Hyperkalaemia, hirsutism, tremors, hypertension, nausea and vomiting, headache, gum hypertrophy, paraesthesiae and hypomagnesaemia are side effects of **ciclosporin**.

**Disulfiram** (antabuse) acts by causing raised acetaldehyde levels. This causes unpleasant effects. Metronidazole and disulfiram synergism may lead to psychosis.

**Digoxin** is slowly absorbed, hence peak effects can be delayed for up to half a day after an **overdose**. Visual disturbance, nausea and vomiting, tachy and bradyarrhythmias can occur with an overdose. Activated charcoal decreases absorption.

**Etanercept** is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the tumor necrosis factor receptor (TNFR) linked to a human IgG1. The receptor binds to TNF, it is not a monoclonal antibody. It is licensed for juvenile rheumatoid arthritis and juvenile idiopathic arthritis. Side effects are septic arthritis, demyelination, pancytopenia, aplastic anaemia and congestive heart failure. .

**Infliximab** is a monoclonal anti-TNF antibody.

**Ezetimibe** acts by prevent cholesterol absorption from the small intestine. Typically it reduces LDL-cholesterol by approximately 20%, triglycerides by up to 5% and raises HDL-cholesterol by approximately 5%.

Ezetimibe is currently licensed for use in combination with a statin in patients who fail to reach desired lipid profiles or as monotherapy in patients intolerant to a statin.

**Thiazides** block Na<sup>+</sup> and Cl<sup>-</sup> reabsorption in the distal tubule. There is usually passive Na<sup>+</sup> and Cl<sup>-</sup> co transport. With this blocked, natriuresis occur. The distal convoluted tubule accounts for 5% of total sodium chloride reabsorption. Thiazides elevate LDL cholesterol, reduce urinary calcium excretion and can cause impotence. Hypercalciuria can be treated with thiazides.

Thiazides can cause thrombocytopenia, hypokalaemia (blocking NaCl channels), and hyperuricaemia.

**Furosemide** acts on the thick portion of the ascending loop of Henle. It inhibits Na<sup>+</sup> and Cl<sup>-</sup> reabsorption there via Na<sup>+</sup>, K<sup>+</sup>, -ATPase-dependent pump. Owing to the large NaCl absorptive capacity of the loop of Henle, agents that act at this site produce a diuretic effect much greater than that seen with other diuretic groups.

**Insulin glargine** is a long-acting insulin analogue, there is a smooth, prolonged absorption profile with no peaks. As such, it is a long-acting agent, suitable for providing a basal level of insulin which mimics the normal physiological state.

Its smooth profile reduces the risk of hypoglycaemia, and when given at night, provides good control of the fasting blood glucose.

**Lofexidine** a centrally acting alpha-2 adrenergic agonist, was launched specifically for symptomatic relief in patients undergoing opiate withdrawal programmes. In open studies in small groups of methadone dependent patients, lofexidine treatment enabled successful detoxification (defined as remaining drug free for 10 days after the last methadone dose) in greater than 65% of patients.

**Mesalazine** can cause neutropenia. It works in IBD by release in the terminal ileum. Mesalazine is given in the acute attacks in Crohn's disease. Sulfasalazine (sulphapyridine and 5-amino-salicylic acid) is used in rheumatoid arthritis.

**Penicillamine** is a DMARD which can be used in Rheumatoid arthritis, Juvenile chronic arthritis and as a copper binder in Wilson's hepatolenticular degeneration. It is also used in PBC, chronic active hepatitis and cystinuria. It can cause aplastic anaemia and thrombocytopenia, proteinuria and loss of taste.

**Penicillamine** is associated with drug-induced lupus, Goodpasture's syndrome, myasthenia, myositis and Stevens-Johnson syndrome.

**Orlistat** is an inhibitor of gastrointestinal lipases, leading to reduced fat absorption. It is licensed for patients with BMI > 28 with associated risk factors, a weight management programme should be in place. Use is not recommended for more than 2 years.

**Quetiapine** is indicated for the management of the manifestations of schizophrenia. The commonest side effects (>5%) are excessive sedation, dizziness, dry mouth, postural hypotension, and elevated ALT.

**Theophylline** is metabolised in the liver. Plasma theophylline levels are increased in heart failure, cirrhosis of the liver, viral infections, elderly patients, and by drugs that inhibit metabolism of theophylline. The plasma levels of theophylline are decreased in smokers, chronic alcoholism and by drugs that induce liver metabolism.

**Metformin** is a biguanide. Its mode of action is thought to be multifactorial and includes delayed uptake of glucose from the intestinal tract, increased peripheral glucose utilisation mediated by increased insulin sensitivity and *inhibition of increased hepatic and renal gluconeogenesis*.

In **metformin** overdose, main symptoms of toxicity include gastrointestinal upset due to a severe lactic acidosis. Hypoglycaemia is not often seen in metformin overdose. If lactic acidosis occurs following overdose, mortality can be high. Management is gastric decontamination and use of activated charcoal if appropriate, and correction of acidosis with 8.4% sodium bicarbonate. Haemodialysis can be considered in severe cases.

**Selective estrogen receptor modulators** (SERMs) exhibit a pharmacologic profile characterized by estrogen agonist activity in some tissues with estrogen antagonist activity in other tissues. The first widely used SERM, **tamoxifen**, has estrogen antagonist activity in breast tissue but shows estrogen-like activity in other tissues. **Raloxifene** is another SERM in clinical use, and it was developed to avoid some of the undesirable estrogen agonist actions of other SERMs to improve the drug safety profile. Raloxifene has been introduced for clinical use in treatment and prevention of postmenopausal osteoporosis.

**Sumatriptan** is a 5HT<sub>1</sub> agonist and may be useful in the treatment of acute migraine attacks. It is available in injectable, intranasal, and oral formulations. **Ergotamine** tartrate is also effective in acute migraine. Propranolol, valproate, NSAIDs,

amitriptyline, pizotifen and gabapentin are effective as prophylactic drugs in migraine.

## IMMUNOSUPPRESSANTS

**Immunosuppressants:** Corticosteroids act on cytosolic rather than cell membrane receptors. Both mycophenolate and azathioprine

Approximately 1 in 300 Caucasians have *thiopurine methyl transferase* (TPMT) deficiency. TPMT is the enzyme that metabolises 6-mercaptopurine and its deficiency results in high risk of **azathioprine** toxicity.

**Azathioprine** is used when steroid withdrawal causes recurrent relapse. Bone marrow suppression (low white cell count) and pancreatitis are side effects of azathioprine

**Methotrexate:** Binding of methotrexate to dihydrofolate reductase reduces nucleotide synthesis as well as amino acids serine and methionine. Folinic acid rescue is usually given after methotrexate therapy (e.g. 24 hours) to reduce myelosuppression side effects.

**Methotrexate** is associated with *interstitial pneumonitis*. This is rare but a serious complication. Chest radiography reveals a diffuse interstitial or mixed interstitial and alveolar infiltrate, with a predilection for the lower lung fields.

Common side effects of **gold** are mouth ulceration, leucopenia, proteinuria and skin rashes.

**Hydroxychloroquine** can cause renal toxicity.

**Sulphasalazine** causes nausea and vomiting, leucopenia and deranged liver function.

**Allopurinol** specifically inhibits xanthine oxidase and prevents metabolism of **azathioprine** to mercaptopurine. This action causes increased toxicity of azathioprine.

## TOXICITY / ADVERSE EFFECTS

Common symptoms of **lithium toxicity** (can occur at levels greater than 1.1 mmol/l) are nausea and vomiting, diarrhoea, disorientation, tremors and ataxia.

**Lithium** can cause hypercalcaemia and hypothyroidism along with a goitre, fine tremor, weight gain, diabetes insipidus and cardiac arrhythmias.

**Gammahydroxybutyric acid** causes hypernatraemia, metabolic acidosis, hypokalaemia, hyperglycaemia.

Hypotension/shock, glucose >8.3 mmol/l, white cell count > 15, haemetemesis and decreased consciousness are features of severe **iron poisoning**.

The primary symptoms of **mercury poisoning** are vague psychiatric ones. Short-time memory can deteriorate. Organic mercury can cross the blood-brain barrier and cause

irreversible nervous system and brain damage, e.g., loss of motor control, numbness in limbs, blindness, and inability to speak.

**Methaemoglobinaemia** can be caused either by a genetic defect in red cell metabolism or haemoglobin structure, or acquired by a variety of drugs and toxins. Common drugs dapsons, nitrates, prilocaine, antimalarials, sulphonamides and dyes. Domestic causes of acquired methaemoglobinaemia include ingestion of food and water high in nitrites and nitrates exposure to aniline dyes in dyed blankets, laundry markings, freshly dyed shoes, red wax crayons and cleaning solution. Standard pulse oximeters give spuriously low readings in the presence of excess methaemoglobin. **Methylene blue** is indicated in any patient with symptoms and/or signs of hypoxia (mental changes, tachycardia, dyspnoea, chest pain). It is contraindicated in G6PD deficiency. High flow oxygen should be administered.

**Carbon monoxide poisoning** is produced by the incomplete combustion of carbon containing fuels such as gas, coal, oil, wood and coke. Headache is the most common symptom (90%) followed by nausea & vomiting, vertigo, alteration in consciousness and weakness. The cherry red skin colour occurs when COHb concentration exceeds 20% but it is rarely seen in life. Pulse oximetry gives falsely high oxygen saturation and it is not recommended.

**Phenytoin** toxicity can cause:

- sedation
- slurred speech
- nystagmus
- ataxia
- vertigo

Long term side effects of **phenytoin** are:

- gingival hypertrophy
- hirsutism
- acne
- coarseness of facial features

Common drugs which can **precipitate a porphyria attack** are:

- Barbiturates
- Sulfonamides
- chloroquine
- steroids

**Barbiturate withdrawal** in an habitual abuser a well recognised cause of fits. Benzodiazepine elevates the level of an inhibitory neurotransmitter, GABA, therefore it serves as a tranquilizer. Barbiturates are prescribed as anticonvulsants, sedatives, and general anesthetics. Commonly abused barbiturates include amobarbital (Amytal), pentobarbital (Nembutal), and secobarbital (Seconal). These drugs depress the respiratory and nervous system functions. *Symptoms of withdrawal syndrome* appear 12-20 hours after the last dose; they include anxiety, irritability, elevated heart

and respiration rate, muscle pain, nausea, tremors, hallucinations, confusion, and seizures.

**Chronic cocaine use** can result in erectile dysfunction, ejaculatory dysfunction, hypersomnia, excitement, emotional instability, restlessness, irritability, apprehension, inability to sit still, teeth grinding, cold sweats, tremors, twitching of small muscles. Severe anxiety and paranoid hallucinations, mania, and psychosis can also occur with cocaine use.

Features of acute **MDMA (ecstasy)** toxicity include agitation, tachycardia, hypertension, dilated pupils, sweating, hyperthermia, disseminated intravascular coagulation (DIC), rhabdomyolysis and acute renal failure.

**Theophylline poisoning** results in profound Hypokalaemia, SVT and VT, vomiting, agitation and convulsions. Activated charcoal is the method of choice for elimination. Diazepam may be used to control convulsions and Propanolol may help tachycardia and reversal of hyperglycaemia (however, beware of using it in asthma).

Agents not adsorbed by **activated charcoal** include:  
metals (lithium, iron)  
hydrocarbons and solvents  
alcohols

**Neuroleptic malignant syndrome** is characterized by fever, muscular rigidity, labile blood pressure, altered mental status, decreased conscious level and autonomic dysfunction. Although potent neuroleptics (eg, haloperidol, fluphenazine) are more frequently associated with NMS, all antipsychotic agents may precipitate the syndrome. For example, these agents are prochlorperazine, promethazine, clozapine, risperidone.

**Dystonic reactions** usually subside within 24 hours following cessation of treatment and can be treated with procyclidine 5-10 mg i.m.

They are well-recognized with dopamine receptor antagonists (neuroleptics). Phenothiazines, prochlorperazine, haloperidol and metoclopramide are examples of drugs which can cause dystonic reactions.

**Oculogyric Crisis** is one of the acute dystonic reactions. It is the most common of the ocular dystonic reactions (which include blepharospasm, periorbital twitches, and protracted staring episodes).

**Priapism** as a side effect is associated with phenothiazines (chlorpromazine), haloperidol, trazodone and alpha blockers (prazosin).

## **MORPHINE EQUIVALENT DOSES**

100 mg of *MST* has the equivalent dose of 25 ug/hr of *fentanyl* over a day.

A 24 hour *diamorphine* dose should be 1/3 of the 24 hour *morphine* dose.

The breakthrough dose of short acting morphine such as *oramorph* should be 1/6th of the total 24 hour dose of morphine.

The equivalent dose of oral *oxycodone* 0.833 is to *diamorphine* SC 1.3 (about 2/3).

## **PREGNANCY**

**Trimethoprim** is a folate antagonist and can increase the risk of neural tube defects. There is relative contraindication for ciprofloxacin in pregnancy due to the possible teratogenic effect. Augmentin, cefaclor, nitrofurantoin and metronidazole are safe in pregnancy.

**Carbimazole** crosses the placenta and can cause nail/finger abnormalities.

**Propylthiouracil** is commonly used in pregnancy instead of carbimazole due to the risks of neonatal hypothyroidism with carbimazole.

**Warfarin** in the first trimester can cause fetal hypoplasia of the nose and limbs. After this period warfarin is associated with neurological damage – mental retardation, microcephaly, optic atrophy and blindness. There is an option to convert from heparin to warfarin in the third trimester, but the patient will have to be re-converted back to heparin before delivery.