Appendix XV

Clinically Important Drug–Drug Interactions

A clinically relevant drug–drug interaction (DDI) occurs when the effectiveness or toxicity of one medication is altered by prior administration or co-administration of another medicine. The potential for clinically important DDIs can often be predicted based on the drug properties, method of drug administration, and patient-specific parameters.

Consequences of drug–drug interactions

There are 3 possible outcomes when drug-drug interactions occur and they are the following:

1. One drug may intensify the effects of the other: Aspirin (anti-platelet) given together with warfarin /coumarin (anticoagulant) increases chances of bleeding; Antihistamines increase the sedative effects of barbiturates, tranquilizers, alcohol and pain relievers.
2. One drug may reduce the effects of the other: Beta blockers used with terbutaline.
3. The combination may produce a new response not seen when either drug is given alone: Alcohol and disulfiram (Antabuse) when taken to either many unpleasant and dangerous responses.

Mechanism of drug interactions

Interactions can be pharmacodynamic or pharmacokinetic. Some drug interactions are due to a combination of mechanisms.

1. Pharmacodynamic drug interactions: Pharmacodynamic interactions are relatively straightforward and are relatively predictable, if the actions of the medicine are known. These interactions are due to competition at receptor sites or activity of the interacting drugs on the same physiological system. There is no change in the plasma concentrations of interacting drugs. These involve the additive effect of similar medicines, or a cancelling effect, for example:

- Increasing risk of hypotension with two antihypertensives
- Antagonism–beta blockers used with terbutaline
- Cephalosporin when taken with aminoglycoside (gentamicin) renal toxicity is increased.
- Corticosteroid, decreases hypoglycaemic action of glipizide, glimepride.

Opposing pharmacodynamic interactions are:
- NSAIDs/antihypertensives or diuretics
- Diuretics/hypoglycaemics
- Steroids/hypoglycaemics
- β-blockers/β-agonists
- CNS depressants/sympathomimetics/caffeine
- Warfarin/vitamin K
- Lithium/NSAIDs

2. Pharmacokinetic drug interactions: Pharmacokinetic interactions are more complex and usually involve interference with
- **Absorption:** Drugs, food and drinks can alter the absorption of drugs. This is one important site of drug interaction, e.g.
  - Antacids, and oral iron preparations block absorption of quinolones, tetracycline, and azithromycin.
  - Iron supplements and the antibiotic or calcium bind together in the stomach, instead of being absorbed into the bloodstream.
  - Ampicillin when taken with food absorption is reduced.
  - Omeprazole when taken with food absorption is reduced.
  - Ampicillin or amoxycillin taken with allopurinol, skin rashes increase.
  - Omeprazole, lansoprazole, H2-antagonists decrease the absorption of ketoconazole, delavirdine.
- **Distribution:** The drug moves from bloodstream into various fluids and tissues or drug may get bound to plasma proteins. One drug may displace another drug from these sites.
- **Metabolism:** Most drugs are metabolized in the liver. The liver has many enzymes that metabolize the drugs and these enzymes can be induced or inhibited by drugs thus causing increase or decrease in metabolism of other drugs:
  - INH inhibits metabolism of carbamazepine.
  - INH induces the metabolism of oral contraceptive resulting in contraception failure.
- **Excretion:** Drugs are excreted primarily by kidneys. One drug may decrease or increase the excretion of drugs. A change in blood concentration causes a change in the drug's effect. If the concentration increases, there may be more adverse effects or if the concentration decreases, there may be lack of therapeutic response.
  - INH inhibits diazepam excretion leading to enhanced diazepam response. Furosemide enhances lithium toxicity.

3. Pharmaceutical interactions: These can be classified as those interactions that occur prior to systemic administration. For example incompatibility between two drugs mixed in an IV fluid. These interactions can be physical (e.g. with a visible precipitate) or chemical with no visible sign of a problem.
- Ketamine is incompatible with barbiturate and diazepam.
- Do not combine thiopentone and suxamethonium.
- Do not combine protamine zinc sulphate and soluble insulin.
- Phenytoin precipitates in dextrose solutions, e.g. D5W.

- Amphotericin precipitates in saline
- Gentamicin is physically/chemically incompatible with most beta-lactams, resulting in loss of antibiotic effect.

4. Drug-food interactions: They are both important and poorly understood. They are important because they can result in toxicity or therapeutic failure.

Decreased absorption: Food frequently decreases the rate of drug absorption and can decrease the extent of absorption. The reduction of rate will simply delay the onset of the effects. But reducing the extent of the absorption reduces the intensity of peak responses.

High-fibre foods can reduce absorption of some durgs. Digoxin, a drug used for cardiac disorders, is reduced significantly by wheat bran, rolled oats, and sunflower seed. Since digoxin has a narrow therapeutic range, reduced absorption can result in therapeutic failure.

Increased absorption: Some drug-food increases the extent of absorption. A high-calorie meal more than doubles the absorption of saquinavir. If saquinavir is taken without food, absorption may be insufficient for antiviral activity.

Impact of food-drug interactions:

- Monoamine oxidase (MAO) inhibitors and foods rich in tyramine (aged cheeses, yeast extracts, Chianti wine), if MAO is combined with these foods can result in life-threatening hypertension.
- Theophylline (an asthma medication) plus caffeine, can result in excessive CNS excitation.
- Potassium-sparing diuretics (spironolactone) plus salt substitutes can result in dangerously high potassium levels.
- Aluminum-containing antacids (Maalox) plus citrus beverages (e.g. orange juice) can result in excessive absorption of aluminum.

5. **Unknown mechanisms:** Not all interactions can be predicted based upon readily recognizable mechanism. Be wary of new combinations where literature is sparse or non-existent.

Risk factors for drug interactions

There are some patient categories that are at greater risk of experiencing a drug interaction. There are also some drugs, which tend to be involved in the more important clinically significant drug interactions.

High-risk patients

Patients on multiple drugs. Higher the number of drugs greater is the risk of drug interactions.

The elderly are more prone to drug interactions, as they are more sensitive to some pharmacodynamic effects and also tend to be on multiple drugs.

Patients with co-morbidities.

High-risk drugs

These include drugs with a narrow therapeutic index, e.g. warfarin, carbamazepine, phenytoin, theophylline and digoxin.

Minimization of drug-drug interactions

Drug-drug interactions are a common problem during drug treatment and give rise to a large number of hospital admissions as a result of medically important, sometimes serious or even fatal adverse events. Drug-drug interactions can also cause partial or complete abolishment of treatment efficacy. Among the various types of medical errors, the occurrence of adverse DDIs is one that is usually preventable. It is, therefore, essential that health professionals be able to evaluate the potential for DDIs and, when detected, to determine appropriate prevention or management strategies.

How to minimize adverse interactions:

- Minimize the number of drugs a patient receives.
- Complete a thorough drug history, including illicit drugs and over-the-counter drugs.
- Risk assessment—as to how common is the interaction? How severe will the interaction be, if it occurs? Is it a dose-related interaction?
- Use alternative drug or adjusting the dosage when an inducer of metabolism is added to or deleted from the patients regimen.
- Adjusting the timing of administration to minimize interference with absorption.
- Monitor for early signs of toxicity when combinations of toxic agents cannot be avoided.
- Be very cautions patient in taking a drug with a narrow therapeutic range.
- Monitor with investigations like INR, blood pressure, liver function tests or clinically for dizziness, muscle aches, etc.

Effect and mechanism of the potential DDIs and options for clinical management

Object drug	Precipitant drug	Effect	Mechanism	Options
Carbam-azepine	**Macrolides** (Eryth-romycin, clarithro-mycin)	Increased carbam-azepine concentra-tions and risk of carbamazepine toxicity	Inhibition of carbamazepine metabolism by CYP3A4	Consider alternative antimicrobials (e.g. azithro-mycin, quinolones, 2nd/3rd generation cephalosporins, penicillin) If alternatives are not appro-priate, monitor carbamazepine concentrations and consider dose adjustment

Object drug	Precipitant drug	Effect	Mechanism	Options
Warfarin	**NSAIDs, Statins** (Simvastatin, Lovastatin), **Antibiotics** (Sulfamethoxazole/trimethoprim, Metronidazole, **Fluconazole**)	Additive risk of bleeding	Antiplatelet effects and GI erosion associated with NSAIDs and the anticoagulant effect of warfarin. Some individual NSAIDs may also alter the pharmacokinetics of warfarin. Statins, antibiotics and fluconazole cause inhibition of warfarin metabolism by CYP2C9.	A non-NSAID alternative such as acetaminophen or opioid analgesics is preferred. If any NSAID is used with warfarin, monitor carefully for evidence of bleeding, especially from the GI tract. Atorvastatin and pravastatin appear to be safer alternatives. Likewise oral penicillins, cephalosporins, quinolones and macrolides are preferred alternatives. If alternatives are not appropriate, carefully monitor the INR, if these agents are started, stopped, or change in dosage then adjust the warfarin dose accordingly.
Tetracyclines (doxycycline, minocycline, tetracycline)	**Antacids** containing Al, calcium, magnesium	Reduced serum concentrations of tetracyclines	Reduced absorption of all tetracyclines	Space administration by 1-2 hours
Ciprofloxacin	**Antacids, sucralfate**, and products containing **calcium, iron, or zinc**	Reduced serum concentrations of ciprofloxacin leading to its therapeutic failure	Interference with the oral absorption of ciprofloxacin	Should be taken either 6 hours before or two hours after the dose of ciprofloxacin
Theophylline	**Ciprofloxacin and erythromycin**	Theophylline accumulation leading to excessive blockade of adenosine receptors and phosphodiesterase resulting in tachycardia and other dysrhythmias, tremors, and seizures	Inhibition of CYP1A2 mediated metabolism of theophylline and thus its increased blood levels.	The dose of theophylline should be reduced, and theophylline plasma concentrations monitored when a patient begins taking ciprofloxacin or erythromycin.
Imipramine, Clozapine	**Fluoroquinolones, Fluvoxamine & Ketoconazole**	Increased level of object drugs (may lead to toxicity)	Inhibition of enzyme CYP1A2 which is responsible for the metabolism of object drugs. Hence their metabolism is decreased.	Monitor concentrations of object drugs or use alternative concomitant drugs which do not interfere with CYP1A2 mediated metabolism

Object drug	Precipitant drug	Effect	Mechanism	Options
Atorvastatin, Cerivastatin, Lovastatin, Simvastatin	**Erythromycin, Clarithromycin, Ketoconazole, Itraconazole, HIV Protease inhibitors (nelfinavir), fusidic acid**	Accumulation of statins leading to diffuse myalgias, rhabdomyolysis and renal failure	Inhibition of CYP3A4 mediated metabolism of statins	Use alternative statins such as Rosuvastatin and fluvastatin which are not metabolized by CYP3A4. Alternatively use other class of antibiotics. However, if use of these antibiotics is unavoidable, start with lowest dose of statins. Monitor for symptoms and signs of myalgia. If myopathy does occur, the statin should be stopped immediately.
Antihypertensives (ACEI, β-blockers, diuretics except CCBs and centrally acting agents)	**NSAIDs** (Indomethacin, naproxen, piroxicam)	Decreased antihypertensive effect	NSAIDs inhibit prostaglandin-mediated vasodilation and promote salt and water retention	Consider alternative analgesics, such as acetaminophen, sulindac, tramadol, or narcotic analgesics or switch to an antihypertensive drug (CCBs) not as susceptible to the blunting effects of NSAIDs. If NSAIDs have to be continued, monitor blood pressure and adjust dose of antihypertensive accordingly.
Oral contraceptive pills (OCP)	**Rifampin, griseofulvin**	Decreased effectiveness of oral contraception	Increased hepatic metabolism of Ethinyl oestradiol in OCP	Avoid rifampin, if possible. If combination therapy is necessary, have the patient take an oral contraceptive pill with a higher oestrogen content (>35 μg of ethinyl oestradiol) or recommend alternative method of contraception.
Acetaminophen	**Carbamazepine, Phenytoin**	Hepatotoxicity of acetaminophen may be increased by high dose or long-term administration of these drugs.	Accelerated CYP450 metabolism of acetaminophen with elevated production of its hepatotoxic oxidative metabolite.	Avoid prolonged coadministration of these drugs. Monitor patient for reduced acetaminophen effects and for signs of hepatotoxicity.
Direct acting Sympathomimetic agents (Epinephrine, Norepinephrine)	**Tricyclic antidepressants (TCAs)-high dose** (amitriptyline, desipramine, imipramine, nortriptyline, etc.)	Increased sympathomimetic effects possible.	Inhibition of norepinephrine reuptake in adrenergic neurons, resulting in increased stimulation of adrenergic receptors.	Limit epinephrine to 0.04 mg with high dose TCAs. Parenteral administration of direct-acting sympathomimetic agents should preferably be avoided. If concomitant use is necessary, initial dose and rate of administration of the sympathomimetic should be reduced, and cardiovascular status including blood pressure should be monitored closely.

Object drug	Precipitant drug	Effect	Mechanism	Options
Clopidogrel	**Proton Pump inhibitors (PPI)** (Omeprazole, Lansoprazole, rabeprazole and esomeprazole except Pantoprazole)	Reduced effectiveness of clopidogrel leading to reduced platelet inhibition	PPIs competitively inhibit one of the principal enzymes, CYP2C19, important in the activation of clopidogrel	Concomitant therapy with PPI and clopidogrel should be avoided. Use of drugs not dependent on the CYP2C19 isoenzyme, such as pantoprazole and H2-receptor antagonists should be preferred.
Diazepam & Phenytoin	**Isoniazid & Ketoconazole**	Increased level of object drugs (may lead to toxicity)	Inhibition of enzyme CYP2C19 by the precipitant drugs. Hence the metabolism of object drugs is decreased.	Monitor concentrations of Phenytoin or use alternative antibiotics which do not interfere with CYP2C19 mediated metabolism
Codeine, β blockers (Propranolol, Atenolol, Metoprolol) Tricyclic Antidepressants (Imipramine, Amitriptyline)	**Fluoxetine, Haloperidol, Paroxetine & Quinidine**	Increased level of object drugs (may lead to toxicity)	Inhibition of enzyme CYP2D6 responsible for the metabolism of object drugs. Hence their metabolism is decreased.	Consider use of alternative concomitant drugs which do not interfere with CYP2D6 mediated metabolism of object drugs
Sulfonylurea hypoglycemics	**Rifampin**	Risk of hyperglycemia	Induces hepatic CYP2C9 mediated metabolism of sulfonylurea and therefore, causes increased clearance	Monitor blood sugar and adjust the dose of antidiabetic drug.