**Drug interactions**

It is usual for patients to receive a number o f drugs at the same time. There are reports of getting 36 different drugs in one admission at John Hopkins Hospital in the United States. A researcher described this as a carrier bag syndrome. When a drug is administered, a response is obtained, if a second drug is given and the response to the first drug is altered, a drug interaction is said to have occurred. Thus, drug interaction is a phenomenon which occurs when the effects of one drug are modified by the prior or concurrent administration of another drug(s). A drug interaction may result in beneficial or harmful effects. However, harmful effects are usually predominated.

Drugs can interact with one another at any point from their being mixed in a pharmaceutical formulation up to their final elimination from the body. Thus, interactions can occur a) outside the body, b) during absorption, c) during distribution, d)at the receptor level (pharmacodynamics), e0 during biotransformation, and f) during excretion.

**Interactions outside the body**

Serious loss of potency can occur from incompatibility between an infusion fluid and a drug that is added to it. Similarly, addition of more than one drug to the same infusion fluid may result in interactions causing loss of activity. The immediate effect of soluble insulin is reduced if it is drawn up with potassium zinc insulin in the same syringe or drip.

**Mixture Results**

Thiopentone +Suxamethonijum Precipitaion

Diaxepam + Infusion fluid Precipitaion

Phenytoin + Infusion fluid Precipitaion

Heparin +Hydrocortisone Inactivation of kanamycin

Carbenicillin +Gentamicin Inactivation of gentamicin

**Interactions during absorption**

Drugs may interact in the gastrointestinal tract resulting in either decreased or increased absorption. Altered absorption may be due to any of the following mechanisms:

Direct chemical interactions between drugs: Antacids containing aluminum, magnesium or calcium form causes chelation with tetracyclines and thereby reduce the bioavailability o f tetracyclines. Similar interactions occur between iron and tetracyclines. Furthermore, Cholestyramine interferes with absorption of thyroxine, digoxin, and warfarin by the process of adsorption.

Altering gastrointestinal motility: Alteration of gastrointestinal motility influences the rate and extent of drug absorption. Anticholinergic drugs and metoclopramide alter the bioavailability of many drugs by decreasing and increasing gastrointestinal motility respectively.

**Mixture Mechanism Results**

Tetracycline +Sodium bicarbonate Altered pH Decreased absorption of tetracycline

Tetracycline + Calcium Chelation Decreased absorption of tetracycline

Tetracycline + Magnesium Chelation Decreased absorption of tetracycline

Tetracycline + Aluminum Chelation Decreased absorption of tetracycline

Tetracycline +Iron Chelation Decreased absorption of tetracycline

Digitalis +Cholestyramine Complex formation Decreased absorption of digitalis

Warfarin + Cholestyramine Complex formation Decreased absorption of warfarin

Thiazida + Cholestyramine Complex formation Decreased absorption of thiazide

**Interactions during distribution**

Displacement from plasma protein binding sites: A drug which is extensively bound to plasma protein can be displaced from its binding site by another drug which has greater affinity for the same binding site, so raising free concentration of displaced drug. Drug like aspirin competes with warfarin for the same protein binding site. Aspirin displaces warfarin from binding site resulting in increased adverse effects of warfarin.

**Bound drug Displacing drug Result**

Bilirubin Sulfonamide Kernicterus

Bilirubin Vitamin K Kernicterus

Tolbutamide Salicylate Hypoglycemia

Methotrxate Salicylate Agranulocytosis

Methotrxate Sulfonamide Agranulocytosis

Warfarin Clofibrate Enhanced anticoagulation

Sulfonamide Salicylate Sulfonamide toxicity

Displacement from other tissue binding sites: When quinidine is given to patients who are receiving digoxin, the plasma concentration of free digoxin is greatly increased because quinidine displaces digoxin from binding sites in the tissue as well as from plasma proteins.

Interactions during biotransformation

Enzyme induction: Enzyme induction by drugs accelerates biotransformation of drugs and is a cause of therapeutic failure. If the drug A is metabolized by the microsomal enzymes, then concurrent administration with a microsomal inducer (drug B) will result in enhanced metabolism of drug A. Anticoagulant control with warfarin is dependent on s steady state of elimination by metabolism. Enzyme induction leads to accelerated metabolism of warfarin, loss of anticoagulant control and danger of therapeutic failure. In contrast, if a patient’s anticoagulant control is stable on warfarin plus an inducing agent by adjustment of danger of hemorrhage then the inducing agent is discontinued because warfarin will be eliminated at a slower rate.

**Primary drug Inducing drug Result**

Warfarin Barbiturate Decreased anticoagulation

Warfarin Rifampicin Decreased anticoagulation

Contraceptives Rifampicin Failure of contraception

Contraceptives Barbiturate Failure of contraception

Quinidine Pheytoin Reduced quinidine effect

Enzyme inhibition: Enzyme inhibition potentiates other drugs whose intensity and duration of action are limited by being metabolized .For example, warfarin metabolism in inhibited by an enzyme inhibitor cimetidine. Thus, cimetidine alters the optimal therapeutic concentrations that were stabilized by a dose of warfarin, resulting in hemorrhage.

**Primary drug Inhibiting agent Result**

Warfarin Metronidazole Hemorrhage

Warfarin Disulfiram Hemorrhage

Phenytoin Isomiazid Phenytoin toxicity

Phenytoin Disulfiram Phenytoin toxicity

Azathioprine Allopurinol Bone marrow suppression

**Interactions during excretion**

Interference with active transport: Probenecid competes with penicillins for active transport process at the kidney and prolongs the action of penicillins, which is beneficial.

**Primary drug Competing drug Result**

Methotrexate Salicylate Increased methotrexate level

Methotrexate Sulfonamide Increased methotrexate level

Salicylate Probenecid Salicylate toxicity

Indomethacin Probinecid Indomethacin toxicity

Lithium Thiazide Lithium toxicity

Digoxin spironolactone digoxin toxicity

Interference with passive diffusion: Alteration of urinary pH influences ionization of drugs and their excretion. Thus, basic drugs are better excreted in acidic urine and acidic drugs are better excreted in alkaline urine. Enhanced excretion of aspirin occurs if sodium bicarbonate is given. Similarly rapid excretion of amphetamine is achieved by giving ammonium chloride.

**Pharmacodynamic drug interactions**

It is quite natural to use two or more drugs at the same time. The use of two or more may produce no effect, synergism or antagonism.

Drug synergism: When the therapeutic or toxic effects of two drugs are greater then the effect of individual drug, it is called synergism. Drug synergism is of two types –additive effect or potentiation.

Additive effect: When the net effect of two drugs used together is equal to the sum of the individual drug effects, the drugs are said t o have an additive effect. For example, the combination of a thiazide diuretic and a beta adrenergic blocking drug is used for the treatment of hypertension.

Potentiation: When the net effect of two drugs used together is greater than the sum of the individual drug effects, the drugs are said to have prtentiation effect. For example, the combination of sulfamethoxazole and trimethoprim is used antimicrobial agents.

**Drug antagonism**

The effects of one drug can be reduced or abolished by the presence of another drug and this effect is termed drug antagonism . Drug antagonism is of three types chemical, physiologicaland pharmacological. Physiological and pharmacological antagonisms involve an interaction of an agonist and an antagonist.

Chemical antagomism: When a drug antagonizes the effect of another drug by simple chemical

reaction without action on the receptor. For example, antacid neutralizes the gastric acid.

Physiological antagonism: When the physiological effect of a drug is antagonized by another drug by acting on two different types of receptors. For example, acetylcholine causes contraction of intestinal smooth muscle by action on muscarinic cholinoceptors. Whereas this action of acetylcholine is antagonized (that is relaxation of the intestinal smooth muscle) by adrenaline. Adrenaline actsby interacting on adrenoceptors.Noradranaline contracts vascular smooth muscle to increase blood pressure, whereas histamine relaxes vascular smooth muscle to decrease blood pressure. Acetylcholine causes constriction whereas adrenaline causes dilatation o fthepupil.

Epinephnne Acetylcholine

Dilated pupil Normal Constncted pupil

Pharmacological antagonism: When a drug antagonizes the effect of another drug by acting on the same receptor it is called pharmacological antagonism.Pharmacological antagonism is of two types competitive and noncompfetitive.

**Competitive antagonism:** Competitive antagonism is reversible. The inhibitory effect of an antagonist id overcome by using large amount o fagonist. Here, both the agonist and antagonist compete for the same receptor and are able to displace each other at the receptor site. For example, acetylcholine causes contraction of intestinal smooth muscle. Atropine blocks this effect of acetylcholine. When a low concentration of an agonist id plotted against the responses, a sigmoid shaped curve will be obtained. The maximum response of the agonist is obtained in the presence of competitive antagonist. The dose response curve remains parallel but is shifted to the right.

Noncompetitive antagonism: The maximum response of an agonist in the presence of antagonist is reduced. The inhibitory effect of a drugs is not overcomed by using large amount of agonist. In this case the antagonist acts at some ratelimiting step of the response distal to the drug receptor complex.