DRUG EFFECTS

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FACTORS MODIFYING DRUG EFFECTS/DRUG VARIATIONS
On administration of a drug, a predicted response is obtained but sometimes

- Individuals may vary considerably in their responsiveness

- Such as: respond differently to drugs both from time to time and from other individuals.

- Some would show less than the usual response, and some may show more than usual response

Occasionally individuals exhibit unusual response

IDIOSYNCRACY
PHYSIOLOGICAL FACTORS

AGE:
Pregnancy
Sex/gender
Body weight
Food
Timings
In new born there occurs

- Decreases acid secretion
- Decreased microsomal enzymes
- Decreased plasma protein binding
- Decreased G.F.R
- There is increase in G.I.T absorption in newborns like ampicillin due to decreased acidity.
- Tetracyclines produce teeth staining in children
- Corticosteroids cause growth and developmental retardation
- Antihistamines cause hyperactivity instead of hypoactivity.
- These are all different responses than adults
Several enzymes are important for drug metabolism, (hepatic microsomal oxidase, glucuronyl and acetyl transferase) have low activity in neonates.

Certain drugs may lead to serious consequences: e.g. chloramphenicol causing gray baby syndrome, sulphonamides causing kernicterus.

Activity of hepatic microsomal enzyme also decreases with age leading prolonged half life of some drugs elderly people: e.g. Benzodiazepines, theophyllines. This may lead to accumulation of drug on repeated doses.
Drug elimination is less efficient in new born babies, and in old people so that drug produces greater and more prolonged effects at extremes of age. Especially drugs which are excreted through kidneys as there is decrease in G.F.R.

- Tubular function is also diminished. E.g., Normal plasma half life of gentamicin is 1-4 hrs, in babies it is 10 hrs and in premature babies it may be up to 18 hrs.

- G.F.R declines to 25% in person of 50 years of age and 50% in person 75 years of age.

- Gentamycin, Digoxin, Pencillins are contraindicated in old people.
PREGNANCY

- Causes several physiological changes that influence drug disposition.
- Volume of drug distribution is increased (total body water may increase by up to 8 liters) providing large space for water soluble drugs. Maternal plasma albumin concentration is reduced, more free drugs will be available.
- Metabolic rate is increased, so the free drugs will be available for elimination.
- Cardiac output is increased, leading to increased renal blood flow and glomerular filtration and increased renal elimination of drugs.
- Lipophilic molecules readily traverse placental barrier. Drugs that are transferred to fetus are slowly eliminated.
Evidences show that men and women may respond differently to same drugs.

This may be due to body size, and amount of body fats.

But there are also some less easily explained differences in gender—specific drug response.

Aspirin shows greater benefit in men than women in cardiovascular diseases.
There appears to be difference in the activity of liver enzymes b/w men and women.

Since the activity of enzymes vary that can result in major difference in drug response.

This difference in liver activity may explain why women routinely wakes up from general anesthesia several minutes before a man given an equal dose.

It has been observed that women with red hair and fair skin are particularly responsive to effects of the analgesic Pentazosin than man of same character.
Addition of mild to moderate hypothermia decreases the systemic clearance of CY450 metabolizes drugs between 7-22% per degree Celsius below 37°C during cooling. The addition of hypothermia decreases the potency and efficacy of certain drugs.

The therapeutic index of certain drugs is narrowed during hypothermia.

Therapeutic hypothermia has shown decrease in neurologic damage in patients experiencing cardiac arrest.
TIMINGS

- It has been observed that endogenous body clock (circadian cycle) may affect the response of the drug.

  e.g.

  In CHD (coronary heart disease) short acting calcium channel blockers seem to be less effective than beta blockers in reducing ischemic events during the night and early morning.
FOOD

Presence of fatty food in stomach delays gastric emptying, the plasma concentration of rifampicin and ampicillin may be much reduced if taken on full stomach

Calcium in milk interferes with absorption of tetracyclines and iron.

Substituting protein for fats and carbohydrates in diet increases drug oxidation rates.
Charcoal grilled beef, cabbage, alcohol increases metabolism

Protein malnutrition affects pharmacokinetics of several drugs.

Citrus flavinoids in grape fruit (but not in orange juice) significantly increases absorption of cyclosporin calcium antagonists and probably other drugs
**PATHOLOGICAL FACTORS**

- **DISEASES** can cause individual variations in drug response.
- **PHARMACOKINETIC VARIATIONS; ABSORPTION:**
  - Gastric and intestinal stasis during an attack of Migraine interferes absorption of drugs
  - Resection of gut may lead to malabsorption of iron, folic acid and fat soluble vitamins and of vit B12 after ileal resection
- Diarrhea increases the motility of the gut and decreases absorption.
- Hypoalbuminaemia from any cause such as nephrotic syndrome, burn, malnutrition, sepsis allows higher proportion of albumin free drug in plasma which is readily available for metabolism and elimination but there can be risk with initial dose for drugs which are to be highly protein bound.
**METABOLISM:**

- Acute and chronic diseases of liver affects the blood flow and function of hepatocytes, leading to decreased drug clearance, and prolong half life.

- Drug metabolism is increased in hyperthyroidism and diminished in hypothyroidism

**EXCRETION**

In acute and chronic renal impairment, concentration of drugs is altered.
PHARMACODYNAMIC VARIATIONS:

- Asthma can be precipitated by beta blocking drugs.
- Raised intracranial pressure, severe pulmonary insufficiency causes patient to be intolerant to opioids precipitate respiratory failure.
- Change in receptors (Myasthenia gravis). Person becomes intolerant to quinine, quinidine and aminoglycoside.
- Increased sensitivity of adrenergic receptors in hyperthyroidism.
GENETIC FACTORS:
These are known as idiosyncratic response
These are rare but very harmful.

- ACETYLATOR STATUS (important for metabolism)
- Slow acetylators: (isoniazid causing peripheral neuropathy on standard dose and pyridoxine is added to T.B regime)
  Rapid acetylators: hepatotoxicity (hepatocellular necrosis) in fast acetylators

- DEFECTIVE CARBON OXIDATION
- may cause poor oxidation of some drugs leading to some adverse effects with standard doses of drugs like beta blockers.

- PSEUDOCHOLINE ESTRASE DEFICIENCY  Failure to rapid inactivation of Suxamethonium, leading to muscular block, results paralysis.
- **G-6-PD Deficiency**: (haemolysis by primaquine) G6PD is necessary to maintain reduced glutathione in red cells and to prevent their hemolysis.
  - This occurs in a small portion of people.
  - Such as chloramphenicol causes aplastic anemia 1 in 50,000.

- **Malignant Hyperthermia**: caused by suxamethonium in prone person due to inherited abnormality in Ca$^{2+}$ release from sarcoplasmic reticulum in striated muscles.)
Pollutants are capable of inducing P450 enzymes, such as hydrocarbons present in tobacco smoke, charcoal broiled meat induce CYP 1A.

Cigarette smokers metabolize some drugs more rapidly than non-smokers.

Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than who are non-exposed.

Polychlorinated biphenyls used in industry, cruciferous vegetables also induce CYP 1A
Grapefruit juice induce CYP3A
OTHER VARIATIONS (QUANTITATIVE)

- More common
- More clinically important
- Patient may be
  - Hypo reactive:
  - Hyper-reactive: to drug to a given dose
- Hypersensitivity:
  - allergic or other immunologic responsiveness to drugs
  e.g. Penicillins
**TOLERANCE**
with some drugs intensity of response to given dose may change during course of therapy, usually decrease in response to continued administration of drug.
e.g. Salbutamol (β-adrenergic agonist)
   Opium , barbiturates , Alcohol
**TACHYPHYLLAXIS:**
when responsiveness diminishes rapidly after administration of drug
e.g. ephedrine
   Amphetamine
**Idiosyncrasy:**

- Is an abnormal genetic response and is usually harmful
- It occurs in small portion of population.

  e.g. aplastic anaemia due to chlormaphenicol
  - haemolysis by primaquine in G-6-PD deficiency
  - Hepatic porphyria by carbamazipine
  - Malignant hyperthermia by suxamethonium
ANAPHYLAXIS

It is an immediate hypersensitivity reaction on exposure to specific antigen leading to life threatening respiratory distress followed by vascular collapse.