ADVERSE DRUG REACTIONS

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WHAT IS AN ADVERSE DRUG REACTION?

World health organization defines Adverse Drug Reaction as:

"Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy."

- From the earliest times, pharmaceutical formulations have been recognized as being potentially dangerous.
- Indeed it is a truism that unless a drug is capable of doing some harm it is unlikely to do much good.
- Public and professional concern about these matters first arose in the late 19th century.
- In 1922, there was an enquiry into the **JAUNDICE** associated with the use of **SALVARSAN**, an organic arsenical used in the treatment of Syphillis.

- In 1937 in the USA, 107 people died from taking an **ELIXIR OF SULFANILAMIDE** that contained the **SOLVENT DIETHYLENE GLYCOL**
- This led to the establishment of the **FOOD AND DRUG ADMINISTRATION** (FDA), which was given the task of enquiring into the safety of new drugs before allowing them to be marketed.
- Major modern catastrophe that changed professional and public opinion towards medicines was the **THALIDOMIDE INCIDENT**.

- In 1961, it was reported in West Germany that there was an outbreak of **PHOCOMELIA** (**hypoplastic and aplastic limb deformities**) in the new born babies.
- It was shown subsequently that thalidomide, a non barbiturate hypnotic, was to blame.
- The crucial period of pregnancy during which thalidomide is TERATOGENIC is the first three months.

- The **THALIDOMIDE INCIDENT** led to a public outcry, to the institution all round the world of **DRUG REGULATORY AUTHORITIES**, to the development of a much more sophisticated approach to the preclinical testing and clinical evaluation of drugs before marketing, and to a greatly increased **awareness of adverse effect of drugs** and **methods of detecting them.**

INCIDENCE OF ADVERSE DRUG REACTIONS

- Many different figures have been published on the incidence of adverse drug reactions. The following are the representing figures.
- **HOSPITAL IN-PATIENTS**:10-20% suffer an adverse drug reaction.
- **DEATHS IN HOSPITAL IN-PATIENTS:** 0.24-2.9% are due to adverse drug reactions.
- **HOSPITAL ADMISSIONS:** 0.3-5% of hospital admissions are due to adverse drug reactions.

DRUGS THAT HAVE BEEN WITHDRAWN OR HAVE HAD THEIR USES RESTRICTED BECAUSE OF ADVERSE DRUG REACTIONS:

Drug	Year	Adverse Reaction	Outcome
Sulfanilamide	1937	Liver damage due to diethylene glycol	Solvent changed; FDA established
Thalidomide	1961	Congenital Malformations	Withdrawn
Chloramphenicol	1966	Blood Dyscrasias	Uses restricted
Benoxaprofan	1982	Liver damage	Withdrawn
Aspirin	1986	Reye's syndrome	Uses restricted
Flecainide	1989	Cardiac Arrhythmias	Uses restricted
Noscapine	1991	Gene toxicity	Withdrawn
Triazolam	1991	Psychiatric disorders	Withdrawn

DRUGS THAT HAVE BEEN WITHDRAWN OR HAVE HAD THEIR USES RESTRICTED BECAUSE OF ADVERSE DRUG REACTIONS:

drug	year	Adverse reaction	Outcome
Temafloxacin	1992	Various serious adverse effects	Withdrawn
Co-trimoxazole	1995	Serious allergic reactions	Uses restricted
Terfenadine	1997	Interactions (e.g. with grapefruit juice)	Withdrawn from OTC sale
Sotalol	1997	Cardiac arrhythmias	Uses restricted
Astemizole	1998	Interactions	Withdrawn
Cisapride	2000	Cardiac arrhythmias	Withdrawn
Cerivastatin	2001	Rhabdomylosis	Withdrawn

CLASSIFICATION OF ADVERSE DRUG REACTIONS

1. DOSE-RELATED ADVERSE DRUG REACTIONS:

a) PHARMACEUTICAL VARIATION

b) PHARMACOKINETIC VARIATION

i. Pharmacogenetic variation
ii. Hepatic disease
iii. Renal disease
iv. Cardiac disease
v. Thyroid disease
vi. Drug interactions

c. PHARMACODYNAMIC VARIATION

i. Hepatic disease

ii. Altered fluid and electrolyte balance

iii. Drug interactions

2. NON-DOSE RELATED ADVERSE DRUG REACTIONS

a) IMMUNOLOGICAL REACTIONS

b) PSEUDO ALLERGIC REACTIONS

c) PHARMACOGENETIC VARIATION

3. LONG-TERM ADVERSE DRUG REACTIONS

a) ADAPTIVE CHANGES

b) REBOUND PHENOMENA

4. DELAYED ADVERSE DRUG REACTIONS
a) CARCINOGENESIS
b) EFFECTS CONCERNED WITH REPRODUCTION
i. Impaired infertility
ii. Teratogenesis
iii. Drugs in breast milk

1. DOSE-RELATED ADVERSE DRUG REACTIONS

- Dose related adverse reactions have led to the concept of the **THERAPEUTIC INDEX**, or the **TOXIC:THERAPEUTIC RATIO**.
- This indicate the margin between the therapeutic dose and the toxic dose.
- The bigger the ratio, the better.
- Examples of drugs with a low **TOXIC:THERPEUTIC RATIO**:
  - *Anticoagulants (warfarin, heparin)*
  - *Hypoglycemic drugs (insulin, sulfonylurea)*
  - *Antiarrythmic drugs (lidocaine, amiodarone)*

- Cardiac glycosides (digoxin, digitoxin)
- Amino glycoside antibiotics (gentamicin, netilmicin)
- Oral contraceptives
- Cytotoxic and immunosuppressive drugs (cyclosporine, methotrexate, azathioprine)
- Antihypertensive drugs (beta adrenoceptors antagonists, ACE inhibitors)

- Dose-related adverse reactions can occur because of variations in the Pharmaceutical, Pharmacokinetic, or Pharmacodynamic properties of a drug, often due to Pharmacogenetic characteristic of a patient.

PHARMACEUTICAL VARIATION

- Adverse drug reactions occur because of alterations in the systemic availability of a formulation

EXAMPLE:

Phenytoin Intoxication, by a change in one of the excipients in the phenytoin capsules from ***calcium sulfate to lactose***, which increase the systemic availability of phenytoin.

- Adverse reaction can occur because of the presence of a contaminant

EXAMPLE:

Pyrogens or even Bacteria in intravenous formulations.

- Out of date formulations can sometimes cause adverse reactions, because of degradation products

EXAMPLE:

out-dated Tetracycline can cause Fanconi's Syndrome.

PHARMACOKINETIC VARIATION

- There is much variation among normal individuals in the rate of elimination of drugs.
- This variation is most marked for drugs that are cleared by hepatic metabolism.
- It is determined by several factors, which may be GENETIC, ENVIRONMENTAL, or HEPATIC.

a) PHARMACOKINETIC GENETIC VARIATIONS:

- Acetylation
- Oxidation
- Succinylcholine hydrolysis

Acetylation:

- Acetylation shows genetic variability.
- There are Fast and Slow acetylators.
- Several drugs are acetylated by **N- ACETYL TRANSFERASE.**
- Fast Acetylation is autosomal dominant and Slow Acetylation is autosomal recessive.

- Drugs whose Acetylation is genetically determined are:
- Isoniazid
- Hydralazine
- Procainamide
- Dapsone
- Some sulfonamides

- Increased incidence of PERIPHERAL NEUROPATHY is observed in slow acetylators of Isoniazid

Oxidation:

- Oxidation also shows genetic variability.
- There are individuals with impaired oxidation and with normal oxidation.
- Impaired oxidation ones are called as POOR METBOLIZERS and the ones with normal are called EXTENSIVE METABOLIZERS.

Debrisoquine type:

- CYP2D6 is a cytochrome P450 enzyme and carries out Debrisoquine hydroxylation.
- Impaired hydroxylation of Debrisoquine is an AUTOSOMAL RECESSIVE DEFECT of this cytochrome.

- Drugs that are affected besides Debrisoquine are:
  - Captopril
  - Metoprolol
  - Phenformin
  - Perhexitine
  - Nortryptine
- Poor hydroxilators are more likely to show **dose related adverse effect** of these drugs.
- In case of **toxic metabolites** risk would be greater in extensive hydroxilators.

Succinylcholine Hydrolysis:

- Succinylcholine is hydrolyzed by **PSEUDOCHOLINESTRASE.**
- In some individuals pseudocholinestrase is abnormal and does not metabolize succinylcholine rapidly.
- In such cases drug persist in blood and continue to produce neuro muscular blockade for several hours. This result in respiratory paralysis called **SCOLINE APNOEA.**
- There are three types of abnormalities of pseudocholinestrase each inherited in an AUTOSOMAL RECESSIVE FASHION.
  - Dibucaine resistant type
  - Fluoride resistant type
  - Silent gene type

b) HEPATIC DISEASE

- Adverse drug reaction due to impaired hepatic metabolism are not so common.
- Hepatocellular dysfunction, as in several hepatitis or advanced cirrhosis, can reduce the clearance of drugs like phenytoin, theophylline and warfarin.
- A reduction in hepatic blood flow, as in heart failure, can reduce the hepatic clearance of drugs that have an high extraction ratio for e.g. propranolol, morphine and pethidine.
- Reduced production of plasma proteins (for e.g. albumin) by the liver in cirrhosis can lead to reduced protein binding of drugs.

c) RENAL DISEASE:

- If a drug or active metabolite is excreted by glomerular filtration or tubular secretion, it will accumulate in renal insufficiency and toxicity will occur.

d) CARDIAC DISEASE:

- Cardiac failure, particularly congestive cardiac failure, can alter the pharmacokinetic properties of drugs by several mechanisms:

1) Impaired absorption, due to intestinal mucosal edema and a poor splanchnic circulation, can alter the efficacy of some oral diuretic, such as FUROSEMIDE;

2) Hepatic congestion and reduced liver blood flow may impair the metabolism of some drugs (e.g. Lidocaine).
3) Poor renal perfusion may result in reduced renal elimination (e.g. Procainamide).
4) Reduction in the apparent volumes of distribution of some cardio active drugs, by mechanisms that are not understood cause reduced loading dose requirements (e.g. Procainamide, Lidocaine, Quinidine)

PHARMACODYNAMIC VARIATIONS

a. HEPATIC DISEASE:

- Hepatic disease can alter pharmacodynamic responses to drugs in several ways;

1. Reduced Blood Clotting:

- In cirrhosis and acute hepatitis, production of clotting factor is impaired and patients bleed more readily.
- Drugs that impair blood clotting, that impair homeostasis, or that predispose to bleeding by causing gastric ulceration should be avoided or used with care for e.g. Anticoagulants and NSAIDS.

2. Hepatic Encephalopathy:

- In patients with, or on the border line of, hepatic encephalopathy, the brain is more sensitive to the effects of drugs with sedative actions. If such drugs are used, coma can result. It is therefore wise to avoid *Opioids* & other *Narcotic Analgesics* and *Barbiturates*.

3. Sodium and Water Retention:

- In hepatic cirrhosis, sodium and water retention can be exacerbated by certain drugs. Drugs that should be avoided or used with care include *NSAIDS*, *Corticosteroids*, *Carbamazepine* and formulations containing large amount of sodium.

b) ALTERED FLUID AND ELECTROLYTE BALANCE:

- The pharmacodynamic effects of some drugs are altered by changes in fluid and electrolyte balance.

Example:

- The toxic effect of cardiac glycosides are potentiated by both Hypokalaemia and Hypercalcaemia.
- The Class1 of Antiarrhythmic drugs such as Quinidine, Procainamide and Disopyramide are more arrhythmogenic if there is hypokalaemia.

2. NON-DOSE RELATED ADVERSE DRUG REACTIONS

- Include

a) IMMUNOLOGICAL and

b) PHARMACOGENETIC mechanisms of adverse reactions.

IMMUNOLOGICAL REACTIONS: (Drug Allergy)

Features of allergic drug reactions:

- There is no relationship to the usual pharmacological effects of the drug;
- There is often a delay between the first exposure to the drug and the occurrence of the subsequent adverse reaction;
- There is no formal dose-response curve;
- The illness is often recognizable as a form of immunological reaction like rash, serum sickness, urticaria etc.

- Factors involved in drug allergy concern the Drug and Patients:

THE DRUG:

- Macromolecules such as PROTEINS (vaccines and enzymes such as streptokinase), POLYPEPTIDES (insulin and dextrans) can themselves be immunogenic.

THE PATIENTS:

- There are genetic factors that make some patients more likely to develop allergic reactions than others:
  - A history of allergic disorders
  - HLA status(antigens on human lymphocytes)

DRUG ALLERGY: A MECHANISTIC APPROACH

- Classified acc. to the classification of hypersensitivity reactions, i.e. into four types, TYPES I-IV.

Type 1 Reactions

(anaphylaxis; immediate hypersensitivity):

- The drug or metabolite interacts with IgE molecules fixed to cells, particularly tissue mast cells and basophiles leukocytes.
- This triggers a process that lead to the release of pharmacological mediators like histamine, 5-HT, kinins, and arachidonic acid derivatives, which cause allergic response.

- Manifest as Urticaria, Rhinitis, Bronchial Asthma, Angio-oedema and Anaphylactic Shock.

- Drugs likely to cause type 1 are Penicillins, Streptomycin, Local Anaesthetics etc.

Type 11 Reactions (Cytotoxic Reactions):

- A circulating antibody of the IgG, IgM, or IgA class interact with an antigen formed by hapten.
- Complement is then activated and cell lysis occurs.

Example: Thrombocytopenia, Haemolytic Anaemia Quinidine or Quinine.

Type 111 Reactions (Immune Complex Reactions):

- Antibody (IgG) combines with antigen i.e. the hapten-protein complex in circulation
- Complex thus formed is deposited in the tissues, complement is activated, and damage to capillary endothelium results.
- Serum sickness is the typical drug reaction of this type.
- Penicillins, Sulfonamides & Antithyroiddrugs may be responsible.

Type 1V reactions (Cell Mediated):

- T-lymphocytes are sensitized by a hapten-protein antigenic complex.
- Inflammatory response ensues when lymphocytes come in contact with the antigen.
- E.g. Dermatitis caused by local anesthetic creams, topical antibiotics and antifungal creams.

Pseudo Allergic Reactions:

- Term applied to reactions that resemble allergic reactions clinically but for which no immunological basis can be found.
- Asthma and Skin Rashes caused by aspirin are the examples.

DRUG ALLERGY : A CLINICAL APPROACH

- Mechanistic approach does not fit in the clinical presentation so a clinical approach.

Fever:

- Drug fever as an isolated phenomenon can occur with penicillin, phenytoin, hydralazine and quinidine.

Rashes:

- Different types of rashes are shown in the table given.

Type of rash	Description	Examples of drugs causing it
Erythema multiform	Target like lesions on the extensor surface of the limbs.	Penicillamine Penicillin Sulphonamides
Erythema nodosum	Tender red nodules, sometimes with bruising on the extensor surface of the limbs.	Phenobarbitals Sulphonamides Oral contraceptives
Exfoliative dermatitis	Red, scaly, Exfoliative lesions sometimes involving extensive areas of skin	Carbamazepine Gold salts Phenylbutazone
Pemphigus	Widespread blistering	Penicillamine Rifampicin
Urticaria	Red raised lesions surrounded by oedema often confluent	Codiene Dextrans Penicillin

BLOOD DISORDERS:

- Thrombocytopenia, Neutropenia, Hemolytic Anaemia, and Aplastic Anaemia can all occur as adverse drug reactions.

RESPIRATORY DISORDERS:

- Asthma occurring as a pseudo allergic reaction to Aspirin, other NSAIDS and Tartarzine is an e.g. adverse drug reaction.

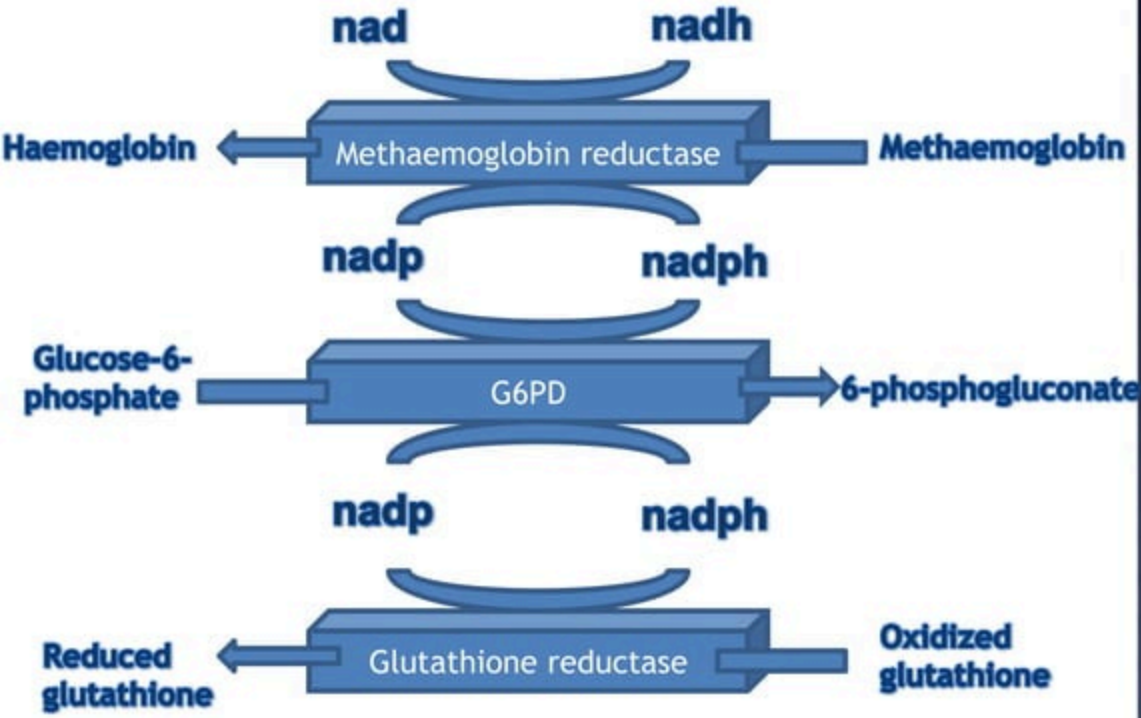
PHARMACOGENETIC VARIATION CAUSING NON DOSE-RELATED REACTIONS

- Red cell enzyme defects
- Porphyria
- Malignant hyperthermia

RED CELL ENZYME DEFECTS:

- Unusual drug reaction occur in individuals whose erythrocytes are deficient in any one of three different but functionally related enzymes.
- **Glucose-6-phosphate dehydrogenase**
- **Glutathione reductase**
- **Methaemoglobin reductase**

FLOW CHART RELATING THREE DIFFERENT ENZYMES



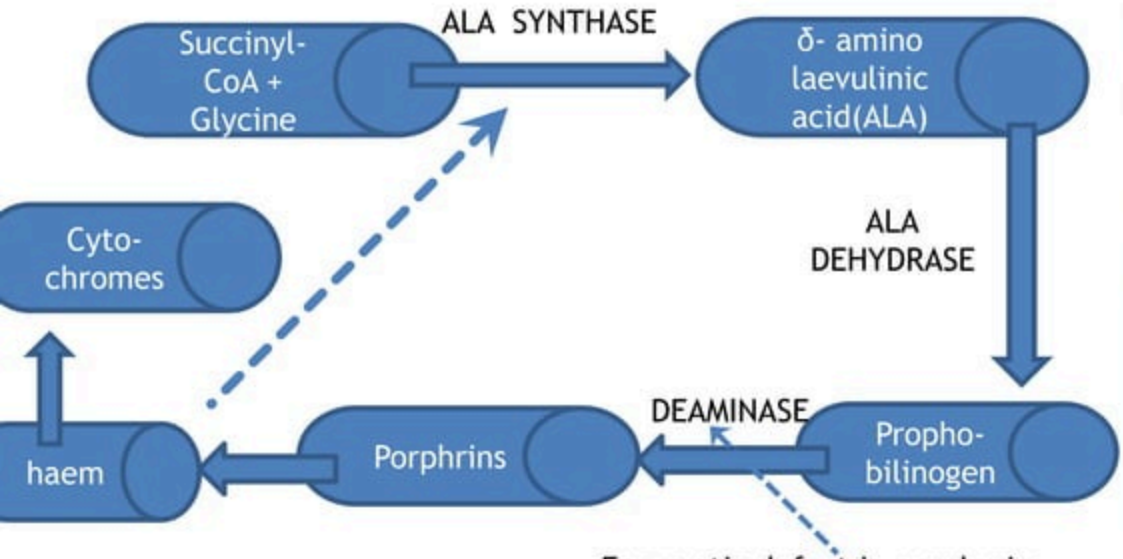
- Glucose-6-phosphate dehydrogenase deficiency:
- G6PD deficient erythrocytes when exposed to oxidizing agents undergoes Haemolysis.
- The prevalence of this defect varies with race.
- There are two varieties of deficiency:
  - ✓ Black variety
  - ✓ Mediterranean variety
- Blacks have normal G6PD production but its degradation is accelerated.
- Mediterranean have abnormal G6PD production.

- **Glutathione reductase deficiency**
  - Deficiency is autosomal dominant.
  - Deficiency of enzyme directly cause deficiency of reduced glutathione.
- **Methaemoglobin reductase deficiency**
  - If Methaemoglobin is not reduced to Haemoglobin continously accumulation of Methaemoglobin takes place resulting in impairment of O_2 delivery to tissues, causing **HYPOXAEMIA**.
  - Inheritance of defect is autosomal recessive.

Porphyria:

- Porphyrias constitute a group of disorders of haem-biosynthesis.
- Different types of porphyrias are there:
  - Acute intermittent porphyrias
  - Variegate porphyria
  - Porphyria cutanea tarda
  - Erythropoietic Porphyria
- Each type of Porphyria is associated with a different abnormality of an enzyme in haem-biosynthetic pathway.
- Drugs to be avoided in porphyria : Barbiturates, Dapsone, Chloramphenicol, Diclofenac etc.

HAEM-BIOSYNTHETIC PAYTHWAY



Malignant hyperthermia:

- It is an autosomal dominant generic disorder of skeletal muscles that occurs in susceptible individuals undergoing General Anesthesia with inhaled agents (halogenated) and muscle relaxants like Succinylcholine.
- This rare condition of uncontrolled release of calcium by sarcoplasmic reticulum of skeletal muscles leads to muscles spasm, hyperthermia and autonomic liability.
- Dantrolene is indicated in life threatening situations.

3. LONG TERM EFFECTS

a. ADAPTIVE CHANGES:

- Examples include development of tolerance to and physical dependence on the **NARCOTIC ANALGESICS** and the occurrence of **TARDIVE DYSKINESIA** in some patients receiving long term neuroleptic drug therapy for schizophrenia.

b. REBOUND AND WITHDRAWAL PHENOMENA:

- During long term therapy sudden withdrawal of the drug can result in rebound reactions.

Examples :

- Typical Syndromes occurring after sudden withdrawal of narcotic analgesic or of alcohol (delirium tremens).
- Sudden withdrawal of Barbiturates result in restlessness , mental confusion and convulsions.
- Sudden withdrawal of ß-adrenoceptors antagonists result in rebound tachycardia which can precipitate myocardial ischemia.
- Sudden withdrawal of corticosteroids results in syndrome of adrenal insufficiency.

4. DELAYED EFFECTS

a. CARCINOGENESIS:

- There are three major mechanisms of carcinogenesis:

i. Hormonal:

- Incidence of VAGINAL ADENOCARCINOMA is increased in daughters of women who have taken STILBOESTROL during pregnancy for the treatment of threatened abortions.
- Increased risk of BREAST CANCERS is about 50% and woman taking HORMONE REPLACEMENT THERAPY (HRT) for more than five years.

ii. Gene Toxicity:

- Occurs when certain molecules bind to nuclear DNA and produce changes in gene expressions.

Examples:

- BLADDER CANCER in patient taking long term CYCLOPHOSPHAMIDE
- Carcinomas of RENAL PELVIS associated with PHENACETIN abuse.
- Non lymphocytic LEUKEMIA in patients receiving ALKYLATING AGENTS such as melphalan, chlorambucil etc.

iii. Suppression of immune responses:

- Patients taking immunosuppressive drugs such as AZATHIOPRINE with CORTICOSTEROIDS have increased risk of developing LYMPHOMAS.

5. EFFECTS CONCERNED WITH REPRODUCTION:

a. Impaired Fertility
b. Teratogenesis

Impaired Fertility:

- Cytotoxic drugs can cause female infertility through ovarian failure with amenorrhea.
- Male fertility can be reduced by impairment of spermatozoal production or function and can be either reversible or irreversible:

- REVERSIBLE IMPAIRMENT can be caused by sulfasalazine, nitrofurantoin, MAO inhibitors and antimalarial drugs;

- IRREVERSIBLE IMPAIRMENT, due to azospermia, can be caused by cytotoxic drugs, such as alkylating agents cyclophosphamide and chlorambucil.

Teratogenesis:

- Teratogenesis occurs when a drug taken during early stages of pregnancy causes a developmental abnormality in a fetus.
- Drugs can affect fetus at 3 stages:

1) **FERTILIZATION AND IMPLANTATION:**

- Conception to 17 days
- Failure of pregnancy which often goes unnoticed.

2) **ORGANOGENESIS:**

- 18 to 55 days of gestation
- Most vulnerable period, deformities are produced

3) GROWTH AND DEVELOPMENT:

- 55 days onwards
- development and functional abnormalities can occur
- ACE inhibitors can cause HYPOPLASIA of organs
- NSAIDs may induce PREMATURE CLOSURE OF DUCTUS ARTERIOSUS

- Different teratogenic drugs are:

- Thalidomide, Methotrexate, Warfarin, Phenytoin, Phenobarbitone, Valproate Sod.,Lithium, etc.

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THANK YOU!!!