ADVERSE DRUG REACTION

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DEFINITION

WHO defines Adverse Drug Reaction as
• A response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy

UK Commission on Human Medicines defines an ADR as
• An unwanted or harmful reaction experienced after the administration of a drug or combination of drugs under normal conditions of use and suspected to be related to the drugs.

EPIDEMIOLOGY

• 4% of hospital admissions
• 1 in 1000 deaths in medical wards
• 10 to 20% of in-patients
• 5% of patients in general practice

CLASSIFICATION

By Rawlin and Thompson

TYPE A
• Known as Augmented
• Occurs Frequently, Less Fatal, Dose Dependent
• Can be cured by DOSE ADJUSTEMENT

TYPE B
• Known as Bizzare
• Occurs Rarely, Not dose dependent, Fatal and mortality can occur
• STOP MEDICATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Sedation</td>
<td>Cholestatic jaundice</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Gastro-intestinal</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Phenytin</td>
<td>Ataxia</td>
<td>Hepatitis, lympadenopathy</td>
</tr>
<tr>
<td>Thiazides</td>
<td>Hypokalaemia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Quinine</td>
<td>Tinnitus</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Bleeding</td>
<td>Breast necrosis</td>
</tr>
</tbody>
</table>
They classify the ADRs as:

- **Type A. (Augmented)**
- **Type B. (Bizarre)**
- **Type C (Chronic)**
- **Type D (Delayed)**
- **Type E (End of Use)**
- **Type F (Therapeutic Failure)**
- **Type G (Genomic or Genetic)**

But More Recent Classification is based on DoTS

- **Dose Relatedness**
- **Time Course**
- **Susceptibility**

### PREDISPOSING FACTORS

**Multiple drug therapy**

- Drug Interaction
- Not always Additive effects

**Age**

- Elderly and Young are more susceptible to ADR
  
  Why Elder?
  - Physiological Changes with ageing.
  - Multiple diseases.
  - Slow metabolism due to decrease blood flow to liver and also decrease in size.
  - Elderly- hypnotics, diuretics, NSAIDS, anti-hypertensives, psychotropics, digoxin

**Gender**

- Females have 1.5-1.7 folds of developing ADR than males.
- Women are prone to develop blood dyscrasias with phenylbutazone & chloramphenicol.
- Histaminoid reactions with neuromuscular blocking drugs.
- Prolongation of QT interval on the electrocardiogram.

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### Alphabetic classification of types of adverse drug effects

<table>
<thead>
<tr>
<th>Type</th>
<th>Type of effect</th>
<th>Definition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Augmented post-acute effects</td>
<td>Adverse effects that are known to occur from the pharmacology of the drug, and are dose-related. They are usually fatal and relatively common.</td>
<td>Hypoglycemia due to sulfonylureas and thiazolidinediones. Homozygous defects in acetylcholine receptors.</td>
</tr>
<tr>
<td>B</td>
<td>Rare effects</td>
<td>Adverse effects that occur unpredictably and often have a high rate of morbidity and mortality. They are uncommon.</td>
<td>Anaphylaxis due to penicillin. Acute hepatic necrosis due to halothane. Dose-related increases in spontaneous mutagenesis.</td>
</tr>
<tr>
<td>C</td>
<td>Chronic effects</td>
<td>Adverse effects that take place during prolonged treatment and may occur with single doses.</td>
<td>Hypersensitivity syndrome with penicillin. Oral dyskinesia due to phenothiazine tranquilizers. Colonic obstruction due to laxatives.</td>
</tr>
<tr>
<td>D</td>
<td>Delayed effects</td>
<td>Adverse effects that occur years from treatment, either in the children of treated patients, or in patients themselves years after treatment.</td>
<td>Second cancers in those treated with alkylating agents. Congenital malformations in infants whose mothers have taken anticonvulsants. Cases of leucocytosis of the newborn and children of women who took diethylstilbestrol during pregnancy.</td>
</tr>
<tr>
<td>E</td>
<td>End of treatment effects</td>
<td>Adverse effects that occur when a drug is stopped, especially when it is stopped suddenly (so-called withdrawal effects).</td>
<td>Unusual anaphylaxis after (1) an intradermal antiserum is suddenly stopped. Allergic contact dermatitis after glycoconjugate vaccine. Such adverse effects are stopped. Withdrawal seizures when anticonvulsants such as phenobarbital are stopped.</td>
</tr>
</tbody>
</table>
PREDISPOSING FACTORS

Intercurrent disease
- Hepatic/renal disease
- HIV – skin reactions with co-trimoxazole
- Critical illness
- Trauma

Race and genetic polymorphism
- Drug metabolizing enzymes (poor, extensive & ultra-rapid metabolizers)
- Drug receptors
- Drug transporters (P-gp or MDR1)

MECHANISM OF DOSE RELATED (TYPE A) REACTIONS

Different doses to produce the pharmacologic effect
Different responses to a defined dose

Pharmacokinetic causes
- Enzyme induction or inhibition – efficacy?
- Genetic variants – oxidation, hydrolysis, acetylation
- Drugs competing for glucuronidation

MICROSOMAL OXIDATION

Drug oxidation occurs mainly in SER of liver by CYP450.

Most commonly used in humans are:
1. CYP1A2
2. CYP2C9
3. CYP2C19
4. CYP2D6
5. CYP2E1
6. CYP3A4
**MICROSOMAL OXIDATION**

CYP2D6 or Debrisoquine hydroxylase polymorphism
(5-10% Europeans)
- Poor metabolizers – reduced first-pass
- Among 65 Drugs metabolized includes psychiatric, neurological and cardiovascular
- Higher incidence of extrapyramidal symptoms seen as AE of antipsychotics metabolized by CYP2D6

**MICROSOMAL OXIDATION**

CYP2C9
CYP2C accounts for 18% protein in human hepatocyte.
Most important is of Warfarin Metabolizing Enzyme.
CYP2C9*1/*1 – normal metabolic rate for warfarin.
CYP2C9*3/*3 – lowest metabolic clearance rate for warfarin.

**HYDROLYSIS**

- Pseudocholinesterase
- Decreased activity in variants leading to suxamethonium apnea

**GLUCURONIDATION**

- Morphine, paracetamol, ethinylestradiol
- Glucuronidtransferases

**ACETYLATION**

- Depend upon the activity of N-acetyltransferase.
- Japanese, Canadian and half of UK are rapid acetylator. (Dose adjustment)
- Slow acetylator = Toxic effects.
- Dapsone, INH, hydralazine, phenelzine, procaainamide, sulfonamides
- Peripheral neuropathy – INH, hematologic AE– dapsone, SLE – procaainamide & hydralazine

**MECHANISM OF DOSE RELATED (TYPE A) REACTIONS**

Renal failure
Digoxin, Ace Inhibitors, Aminoglycosides Antibiotics, Class I Anti-arrhythmic Drugs (Disopyramide, Flecainide) And Cytotoxic Agents
MECHANISM OF DOSE RELATED (TYPE B) REACTIONS

Pharmacological causes
- Presence of degradation products of the active constituents
- Excipients

MECHANISM OF DOSE RELATED (TYPE B) REACTIONS

Pharmacokinetic causes
- P-glycoprotein / MDR1 – found in the cells of gut wall, surface of hepatocytes & renal tubular cells

MECHANISM OF DOSE RELATED (TYPE B) REACTIONS

Pharmacodynamic causes
- Presence of degradation products of the active constituents
- Excipients

HEREDITARY METHEMOGLOBINEMIAS

- Methemoglobin reductase – cyanosis
- Drugs to avoid
  - Dapsone
  - Nitazoxanide
  - Primaquine
  - Quinolones (ciprofloxacin, nalidixic acid, norfloxacin, ofloxacin)
  - Sulfonamides (Cotrimoxazole)

PORPHYRIAS

- Inherited disorder (autosomal) in heme biosynthesis
- Abdominal and neuropsychiatric disturbances
- Excretion of excessive amounts of porphyrin precursors 5-ALA (aminolevulinic) or porphobilinogen
- Drugs that induce ALA synthase.
MALIGNEANT HYPERTHERMIA

- Rapid rise in body temperature (at least 2°C per hour)
- Associated with anesthetics and muscle relaxants (succinylcholine)
- Stiffness of skeletal muscle, hyperventilation, acidosis, hyperkalemia, increased activity of sympathetic NS
- Increase level of Ca²⁺ Release.
- Antidote: Dantrolene

ABNORMAL IMMUNOLOGICAL RESPONSE

It is defined as an adverse reaction to a drug by a specific immune response either directly to the drug or one or more of its metabolites alone or to a drug bound to a body protein such as albumin. (Hepatitis).

Features:
- No relation to the usual pharmacologic effects of the drug
- Delay between the 1st exposure to the drug and subsequent appearance of the ADR
- Small doses may elicit the reaction once the allergy is established
- Reaction disappears on withdrawal
- Illness is often recognizable as a form of immunologic reaction
- Often include a rash, angioedema, the serum sickness syndrome, anaphylaxis and asthma which are reactions similar to those of classical protein allergy

Hyperesensitivity Reactions

<table>
<thead>
<tr>
<th>Type</th>
<th>Antigens</th>
<th>Mediators</th>
<th>Diagnostic tests</th>
<th>Time taken for reaction to develop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (immediate)</td>
<td>Pollens, molds, yeasts, drugs, food and passive</td>
<td>IgE, mast cells</td>
<td>Skin prick test, skin reactivity test (e.g. tuberculin test)</td>
<td>5-15 min</td>
</tr>
<tr>
<td>2 (cytokine)</td>
<td>Cell surface or tissue bound</td>
<td>IgG, IL-2 and complement</td>
<td>Coombs' test, indirect immunofluorescent antibody test</td>
<td>24-48 hours</td>
</tr>
<tr>
<td>3 (immune complex)</td>
<td>Opsonophagocytic test (opsonins), IgG, IgM, IgA</td>
<td>Complement, immune complex</td>
<td>Indirect immunofluorescent antibody test</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td>4 (type delayed)</td>
<td>Cell-surface receptors</td>
<td>Skin tests, nerve biopsy, histology</td>
<td>Round cell infiltration, cell surface granules</td>
<td>24-48 hours</td>
</tr>
</tbody>
</table>

\# Type V hypersensitivity may also be classified with type II reactions

DELAYED ADVERSE EFFECTS

- Pigmentary retinopathy – phenothiazine
- Vaginal carcinoma – stilbestrol
- Malignancy – immunosuppressives and chemotherapeutic agents

MALIGNANT HYPERTHERMIA

- Glucocorticoid glaucoma
- Cholestatic jaundice induced by oral contraceptives
ADVERSE EFFECTS ASSOCIATED WITH DRUG WITHDRAWAL

- Benzodiazepine withdrawal syndrome
- Rebound hypertension – clonidine
- Acute adrenal insufficiency - corticosteroids

IDENTIFICATION OF ADR

1. A careful drug history is essential.
2. Provocation testing.
3. Serological testing and lymphocytes testing.
4. Stop all potentially causal drugs and reintroduce them one by one until the drug at fault is discovered.