ADVERSE DRUG REACTIONS: IDENTIFICATION, MANAGEMENT AND REPORTING SYSTEM

Prof. Rakesh Kumar Tewari,
M.D.(Ay.) I.M.S.(BHU),
Head, Deptt Of Dravyaguna,
Govt. Ayurveda College, Jhansi (UP).

E mail: vdrakesh.tiwari@gmail.com
IMPORTANCE OF KNOWING ADRs

Although in public opinion ASU Drugs are considered to be natural, safe, harmless, risk free, can be used without medical supervision, virtually for effective and safe drug therapy it is important to know :-

- Nature and severity of ADR.
- Whether treatment has to be stopped or not?
- How safe the drug is?
- How it may be made more safe and acceptable to patient?
MEASURE OF SAFETY:
THERAPEUTIC INDEX (T. I.)

T.I. = \[ \frac{LD_{50}}{ED_{50}} \]

Drugs with a T.I. of:
- 10 or more - safe.
- 3 or 4 - must be used cautiously.
- < 3 - cannot be used safely.

Note: T.I. for same drug may be different in different clinical situations e.g. T.I. for Aspirin in headache is more than its T.I. for Antiarthritic and Antirheumatic uses (dose 0.3 to 1g/day as compared to 5 to 10g/day respectively).
SITES OF UNWANTED EFFECTS

• LOCAL - At the site of contact- e.g. –nausea, vomiting, dia. with many oral drugs.

• FOCAL - At a particular organ e.g. - Cardio toxicity of emetine, nasal stuffiness due to Jatamansi Fant.

• GENERAL - Widespread e.g. – body ache, fatigue, fever, allergic rashes etc.
TYPES OF UNWANTED EFFECTS

- SIDE EFFECTS
- TOXIC EFFECTS
- SECONDARY EFFECTS
- INTOLERANCE
- IDIOSYNCRASY OR PHARMACOGENETIC EFFECT
- HYPER SENSITIVITY
- SPECIAL TOXICITIES
SIDE EFFECTS

Normal pharmacological effects in therapeutic doses.
Can occur in all.
Undesirable but unavoidable.
Usually do not need withdrawal of drug.
  e.g.- Phenobarb in epilepsy – drowsiness.
  Atropine & parsik yavani for abd. colic – dryness of mouth.
  Isoprenaline & somalata churna for br. asthma – palpitation.
  Diuretics – postural hypotension & hypokalemia.
S/E can be used as therapeutic effects in some conditions.
Mild constipating effect of Ashwagandha in IBS improves its adaptogenic action.
TOXIC EFFECTS

Dose related undesirable pharmacological actions or due to therapeutic dose in an intolerant person or due to prolonged use of cumulative drugs.

May need – Dose reduction / Withdrawal of the drug.

- **Absolute:** due to real excess/ accumulation of drug.
- **Relative:**
  1. decreased biotransformation/ excretion.
  2. Excess response in normal dose due to abnormal physiological variables.
     e.g. Digitalis toxicity in hypokalemia.
  3. Therapeutic dose in an intolerant person.
     e.g. Hepatotoxicity by some steroids, i.v. Tetracyclines, Nephro/ototoxicity by Amino glycosides, cardio toxicity by emetine etc.
INTOLERANCE/ HYPER-REACTIVITY

Excessive but expected pharmacological response due to biological variation.

e.g. Sedative dose of pnenobarb leading to severe CNS depression.
IDIOSYNCRASYSY or PHARMACO – GENETIC EFFECT

Unexpected & abnormal pharmacological response due to Genetic peculiarity.

Example:

- Haemolysis with primaquine, sulfones & sulphonamides (G-6-PD deficiency)
- Succinylcholine Apnoea (due to atypical pseudo cholinesterase)
- Cinchonism with Quinine & quinidine
- Salicylism with salicylates.

Note: Therapy may have to be stopped or dose to be titrated.
HYPERSENSITIVITY REACTIONS or ALLERGIC REACTIONS

Qualitatively abnormal response
Not related to pharmacological response
Not related to dose
Based on Antigen Antibody Reaction
Requires prior sensitization to drug
(Direct exposure or indirectly through food or environmental factors)
Drugs act as partial antigens (HAPTENs) which combine with body proteins & become complete antigens.
HYPERSENSITIVITY REACTIONS or ALLERGIC REACTIONS

Antigen or Allergen may be – 1. Drug itself
3. Preservative / vehicle.
4. contaminant/adulterant

Classification: (on the basis of +ve skin tests with antigens)

• Immediate Type – Type I, II & III.
• Delayed Type – Type IV.
TYPE – I HYPERSENSITIVITY REACTION : ANAPHYLAXIS

IgE (Reaginic Ab) fixed on mast cell surface react with Ag and release mediators without cell injury. Symptoms appear within minutes & last for 1-2 hr.

Mild forms – Urticaria & Agio-neurotic oedema with food allergens & several drugs. Asthma & Rhinitis with Aspirin, Sulphonamides & Penicillins etc.

Severe Form: ANAPHYLACTIC SHOCK – rare life threatening reaction seen with penicillins, vaccines/ sera etc. Leading to Bronchospasm, Laryngeal oedema, hypotension and shock.

Treatment – Airway patency, Adrenaline, Corticosteroids, Pressure Agents & management of shock.
TYPE II: CYTOTOXIC HYPERSENSITIVITY / AUTO – ALLERGY

Failure of recognition of own tissue is lost due to partial antigenic action of drugs
Antibodies formed against body tissues activate surface bound COMPLEMENT SYSTEM leading to PHAGOCYTOSIS of target cells.
e.g.- Thrombocytopenic purpura – by Allopurinol, pbz, quinidine, sulfa drugs.
• Haemolytic Anaemia – Alpha – M- DOPA, L-DOPA, Penicillin, Quinidine.
• Agranulocytosis – Chloramphenicol, Sulforamides, Pbz, Alpha-M-DOPA
• Collagen Diseases (SLE, RA) – Hydralazine, Phenytion, INH etc.
TYPE III – IMMUNE COMPLEX MEDIATED HYPERSENSITIVITY

COMPLEMENT, IgG & IgM react with Antigen - Liberate vaso-active substances and Lysozymes leading to cell damage.

• Arthus Reaction – Localised tissue necrosis due to Acute Immune complex Vasculitis at the site of entry of antigen
• Serum Sickness –
  Fever, skin rash, Lymphadenopathy and Arthralgia
  Onset is delayed.

Treatment may have to be stopped.

• Drug Fever – Sudden high grade fever, 7 to 21 days after administration of drug.

• e.g. – from Antivenom /sera, Penicillins, Phenytoin, Sulfonamides etc.
TYPE – IV CELL MEDIATED HYPERSENSITIVITY

Reactions is initiated by exposure of sensitized T cells to specific Antigen.

- **Delayed type hypersensitivity** - Activated Memory T cell recruits other cells (Macrophages) which phagocytose & destroy the target cell bearing Antigen.

- **T cell mediated cytotoxicity** - Sensitized CYTOTOXIC T Lymphocytes kill Ag bearing target cells directly. e.g. *Cutaneous Reactions* (Dermatitis) from Penicillins & topical sulphonamides.

  - **Aplastic Anaemia** from chloramphenicol, Phenylbutazone.

  - **Hepatotoxicity** - Hepatitis type – by INH, Pyrazinamide, Halothane.

  - Cholestatic type – by Phenothizines.
FACTORS FAVOURING ADRs

(A) Non drug Factors
   (i) Intrinsic to patient – Age, sex, personality, habits, genetic factors, Immune status.
   (ii) Extrinsic to patient

   Environment

   Prescriber
   (a) Inappropriate choice of drug.
   (b) Unskilled administration

(B) Drug Factors
   (1) Intrinsic to drug – Unwanted effects
   (2) Drug Interactions
ADVERSE EVENT / ADVERSE EXPERIENCE

Any untoward occurrence (clinical phenomenon) that may present during treatment with a pharmaceutical product but which does not necessarily have causal relationship with this treatment.

SIGNAL / ALERT

Reported more than one adverse event may lead to generate a signal depending upon the seriousness of event & quality of information.
ADVERSE REACTION
A response to drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. (WHO Technical Report No. 498 (1972))

UNEXPECTED ADRs – nature & severity is not consistent.

SERIOUS ADR
- Results in death/disability/incapacity.
- Is life threatening?
- Requires hospitalisation or prolongation of existing hospitalisation.
AIMS OF ADR REPORTING

1. To identify, quantify & document drug related problems.
2. To increase knowledge & minimise such episodes.

WHAT TO REPORT

1. All suspected ADRs
2. Lack of efficacy
3. Counterfeiting
4. Resistance
5. Interactions
6. Dependence & Abuse.
REPORTING OF ADVERSE DRUG REACTIONS

1. Notifier
2. Reporter - any healthcare professional.
3. Where to report? –
   - Peripheral pharmacovigilance centre
   - Regional pharmacovigilance centre
   - National pharmacovigilance resource centre

- How to report- in Reporting form for suspected ADRs
- What happens to information submitted – information is handled confidentially. PPC forwards the form to RPC who will carry out causality analysis. Information forwarded to NPRC will be analyzed & forwarded to Deptt. Of AYUSH, Govt of India.
Concept of ADRs in Ayurveda

आौषधं द्वानभिज्ञातं नामरूपगुणैस्त्रिभि:।
विज्ञातं चापि दर्प्युक्तमन्थायोपपद्यते॥
योगादिपविषं तीक्ष्णमुत्तमं भेषजं भवेत्॥
भेषजं चापिदर्प्युक्तं तीक्ष्णं संपद्यते विषम्॥

च०सू० 1/126॥

तेषां कर्मेऽशु बाह्योऽशु योगमाध्यमतरेषु च ।
संयोगं च प्रयोगं च योवेद स भिषगवरः ॥
प्रयोगः शमयेद् व्याधिः योजन्यमन्यमुदीर्येत्॥
नासो विशुद्धः, शुद्धस्तु शमयेद्यो न कोपयेत्॥

च०सू० 1/127॥

च०सू० 4/29॥

च०नि० 8/23
इदमेवप्रकृत्यैवंगुणमेवप्रभावमस्मिन् देशेजातमस्मिन्नृतावेव
गृहीतमेवनिहितमेवमुपस्कृतमनया च मात्रया युक्तमस्मिन् व्याधावेवविधधस्य
पुरुषस्यैवतावन्तंदोषमपकर्षत्युपशमयति वा,
यदन्यदपिचैवविधश्वपेषजंभवेतच्यानेनविशेषेण युक्तमिति ॥

च०वि०८/८७ ॥
PATIENT FACTORS

तस्मादातुरंपरीक्षेत् प्रकृतितत्वः, विकृतितत्वः, सारतत्त्वः, संहननतत्त्वः,
प्रमाणतत्त्वः, सात्म्यतत्त्वः, सत्यतत्त्वः, आहारशक्तितत्त्वः,
व्यायामशक्तितत्त्वः, वयस्तत्त्वेति, बलप्रमाणविशेषग्रहणहेतोऽऽऽ

च०विः ९४ ॥
ADRs/Unwanted effect /Contra indications of some drugs described in Bhav Prakash

हरीतकी, आमलकी, पिप्पली, रसोन, गुगुलु, शुण्ठी, सूरण, पनस, धान्यक, शतपुष्पा, कुलत्थ, अतसी, प्रसह।
Conclusion

- Hospitalization due to drugs is about 6-7% of total admissions.
- It is very expensive.
- Do not force govt. physician to prescribe particular medicine (e.g. kaishor guggulu in place of kanchnar guggulu.)
- Minimize multi drug prescription.
- Please listen to your patient.
Acknowledgement

Dr. Ram Milan
Dr. Rajeev Kushwaha
Department of Dravyaguna
Bundelkhand Govt Ayurvedic College, Jhansi (U.P.)