Patient Safety

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REASONS FOR RISK TO PATIENTS SAFETY THROUGH DRUG USE

- **Inherent safety issues of drugs**
- Quality issues--use of Sub-standard/ adulterated/ misbranded /spurious drugs.
- Misuse and abuse of drugs
- Human / Prescription errors
- In-appropriate off-label use.
- Patient non-compliance

Source of Information on Drug Safety

a) **Pre-clinical/ Non-Clinical studies**

b) **Clinical studies**

During the Clinical drug development stage (pre-marketing)

Post-marketing Stage.

c) **Reports of ADRs**

Within the country

From other country

Medical Journals

WHO Bulletins

d) **Epidemiological studies**

Case Control

Cohort

LIMITATION OF CLINICAL TRIAL-- 1

- Assessment of safety and efficacy of the drug are generally based on data from a limited number of patients,
- Many studied under the controlled conditions of randomized trials.
- Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials,
- Long-term treatment data are limited.
- Moreover, patients in trials are closely monitored for evidence of adverse events.

LIMITATION OF CLINICAL TRIAL-- 2

In actual clinical practice -

- Monitoring is less intensive,
- A broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities),
- Events too rare to occur in clinical trials may be observed (e.g., severe liver injury).
- These factors highlight the need for Pharmacovigilance for continuing analysis of relevant safety throughout the lifecycle of a drug.
- This includes detection of adverse effects during the clinical trial and post marketed phases, monitoring and updating the risk-benefit ratio based on relevant findings, prevention or minimization of adverse effects of drugs.

DRUG REGULATION TO ENSURE PATIENT SAFETY IN INDIA-- 1

- 1982-Section 26A and Section 10A of Drugs & Cosmetics Act, 1940 empowering Govt. of India to prohibit manufacture/import of any drug, use of which is likely to involve any risk to human beings or animals or that the drug does not have therapeutic value claimed for it.

- 1988–Rule 122A, 122B, 122C, 122D, 122E & Schedule Y of Drugs & Cosmetics Rules requiring clinical trial for evaluation of safety & efficacy before approval of new drugs.

- 2001-New Drugs permission to manufacture or import of a new drug was subject to post marketing surveillance study during initial period of two years of marketing the new drug after getting protocols etc. approved by LA.

DRUG REGULATION RELATING TO PATIENT SAFETY IN INDIA-- 2

- 2005-Schedule Y was amended requiring close monitoring of new drugs for their clinical safety once they are marketed and mandatory submission of Periodic Safety Update Reports (PSUR).
- 2008-Section 26A was amended subsuming the word, "Prohibit" with "regulate, restrict or prohibit" and a Section 26B was introduced to regulate or restrict drug in case of emergency situation
- 2011-The condition of new drug permission for PMS was amended requiring the firm to furnish PSUR.
- 2013 - Rule 122DAB and Appendix XII OF Schedule Y regarding procedures for examination of SAEs of injuries and deaths occurring in clinical trial and payment of compensation
- 2016- Regulation requiring the manufacturer of new drugs to have a pharmacovigilance system in their organisation managed by Medical Person or Pharmacist with relevant experience

Rules relating to compensation in case of related SAEs incorporated in 2013 and 2014

- Rule 122DAB and amendment in Schedule Y
  - Medical Management in case of any injury
  - Examination of SAEs,
  - Provisions for payment of compensation in case of clinical trial related injury or death
  - Expansion of responsibilities of Investigator, Sponsor and EC,
  - Amendment in ICD.

Other measures to protect the rights of CT subjects

- Independent Expert Committees have been constituted to examine the reports of deaths in clinical trials.
- The committee has prepared following formula for determining the quantum of compensation in case of clinical trial related deaths

Compensation = (B x F x R)/ 99.37

Where,

B = Base amount (i.e. 8 lacs)

F = Age Factor (based on Workmen Compensation Act)

R = Risk Factor of the subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

1 .0.50 terminally ill patient (expected survival NMT 6 months)

2. 1.0 Patient with high risk (expected survival between 6 to 24 months)

3. 2.0 Patient with moderate risk

4. 3.0 Patient with mild risk

5 4.0 Healthy Volunteers or subject of no risk

However, in case of patients whose expected mortality is 90 % or more within 30 days, a fixed amount of Rs. 2 lacs should be given.

Other measures to protect the rights of CT subjects

- Formulae to determine quantum of compensation in case of SAE of injury other than death have been prepared.

Considering the definition of SAE, the following sequelae other than death are possible, in which the subject is entitled for compensation:

a) A permanent disability
b) Congenital anomaly or birth defect
c) Chronic life-threatening disease or
d) Reversible SAE in case it is resolved.

The formulae for the above four situations have been worked out by the Committee, which has been approved by the MOHFW .

PROCEDURE FOR RESTRICTION / PROHIBITION OF DRUGS

- Consideration of safety issues reported in the published literature, in PvPI or in any country or restriction on use /withdrawal of any drug in any country due to safety or other reasons
- Examination by Expert Committees /DTAB to review the status of the drug formulation.
- The use of the drug is assessed on the basis of
  - available technical information
  - benefit -risk ratio,
  - local needs and
  - availability of the safer alternatives etc.
  - Recommendation of the committees are forwarded to the Ministry for consideration and action
  - Restriction /prohibition through Gazette Notification by the Ministry

CASE EXAMPLE-- Dextropropoxyphene

- First introduced in USA as an analgesic half a century ago.
- In India, the drug was introduced more than forty years ago
- Withdrawn from US market in September 2010 for serious toxicity to the heart
- On 25 June 2009 the CHMP of EMA- benefits do not outweigh its risks, and medicines should be withdrawn throughout the European Union (EU).
- Similar action in Canada, UK etc.
- Therefore, the manufacturing and marketing of the Dextropropoxyphene and it formulations put under suspension on 23.05.2013 till the safety of the drug is examined and established in the country.

Dextropropoxyphene

- Subsequently an expert Committee discussed the issue in detail and recommended that suspension of DPP should be revoked subject to the following conditions:
- Should be used in cancer patients only;
- The label, package insert, promotional literature etc.
  - **Should clearly mention the following warning**:

    Warning: "For use in cancer patient only".
- The committee also recommended that the drug should be considered for banning in six months, if manufacturers do not follow the above conditions for marketing.

The matter has also been deliberated by the DTAB

However, the manufacture, sale of the drug is still under suspension

Case example-FDC OF Flupenthixol and Melitracin

- FDC of Flupenthixol 0.5mg with melitracen 10mg was approved on 28.10.1998
- In, 2011, concerns were raised regarding its approval
- The issue were examined by various expert Committees
- In 2013, NDAC recommended for suspension and manufacture and sale of the drug was suspended on18.6.2013 under section 26A
- The manufacturer challenged the recommendation of the NDAC and the notification in one High Court
- The Court passed order that the notification and the recommendation of the NDAC stand quashed subject to the observation and liberty to reconsider afresh and take a decision one way or the other in accordance with law
- Thereafter expert committee and DTAB examined and recommended that the use of FDC of Flupenthixol + Melitracen should be discontinued in the country
- Finally, the drug was prohibited in the country on11.7.2014

Case example- Pioglitazone

- Based on the regulatory action in France and Germany and report of 8 cases of bladder cancer in the country , marketing of pioglitazone was suspended in the country

- The Expert Committee after detailed deliberation on the issue of safety of pioglitazone & its suspension, recommended that the suspension should be revoked. However,the drug should be allowed to be marketed in the country with various restrictions

- Based on the recommendation, notification was issued allowing the marketing of the drug subject to various safety restrictiopns


Thank you