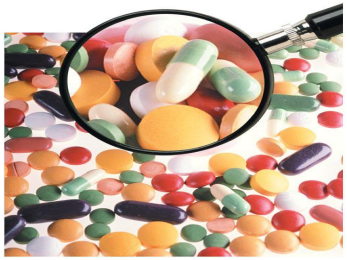


Pharmacovigilance

Dr. Anjan Adhikari
Associate Professor
Department of Pharmacology
R G Kar Medical College & Hospital
Kolkata

Dying from a disease is sometimes unavoidable; dying from a medicine is unacceptable.

Lepakhin V. Geneva 2005

Voice of the Patients

"Keep Me Safe"

"Get Me Well"

"Treat Me Nice"

Jamie Orlikoff

“First, do no harm”

Pharmacovigilance

- **It is an umbrella term used to describe the process of monitoring and evaluating ADRs – is a key component of effective drug regulation systems, clinical practice and public health programmes**

Hindustan Times

January 13, 2003

IMA ends debate: Nimesulide is safe

Arun Kumar and Sutirtho Patranobis New Delhi

More than 50 doctors country-wide participated in an **opinion poll** organised by the IMA and submitted **data** on the use of nimesulide on nearly 5.3 lac patients.

The **data clearly showed** that the side-effects of the drug were nothing more than common GI problems …

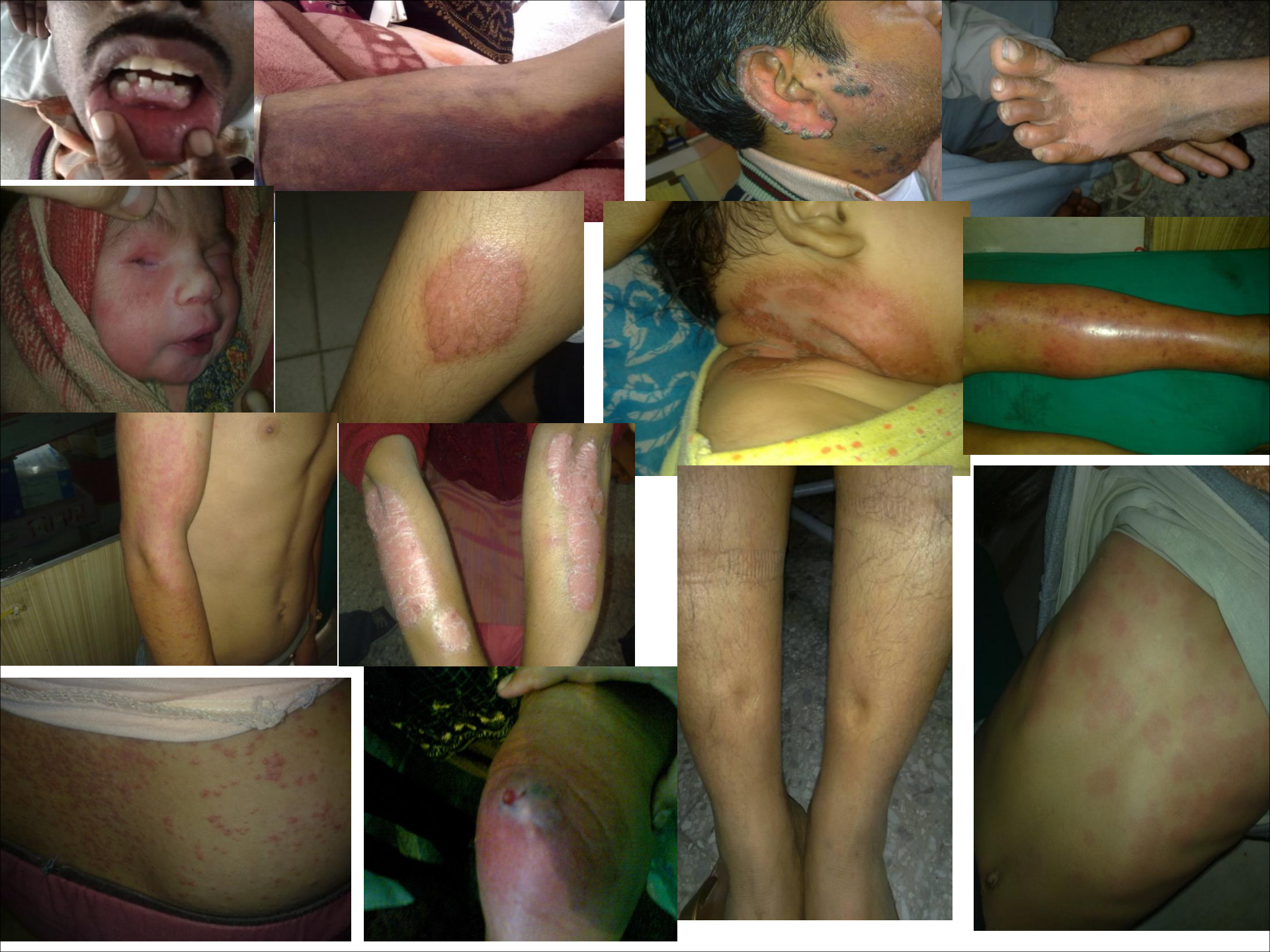
THE TIMES OF INDIA

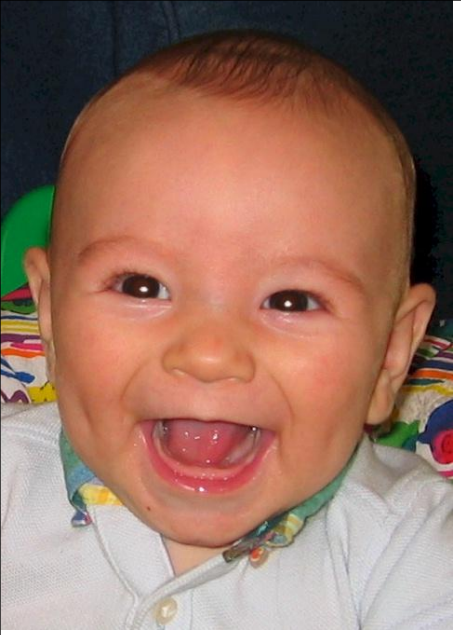
Nimesulide not safe, *insist* doctors

By Kalpana Jain **Times News Network**

New Delhi: Doctors have questioned an **"opinion poll"** conducted by the Indian Medical Association (IMA) to declare the controversial fever drug, Nimesuilde, "safe".

… a leading paediatrician who is the former head of the pediatrics department at the All India Institute of Medical Sciences, told The Times of India … that severe side effects of the drug have been **documented** and it needs to be used with caution.





Why we are so concern about safety of Drugs ?

- Drugs can do good
- Drugs can do harm
- Whenever a drug is taken a risk is taken

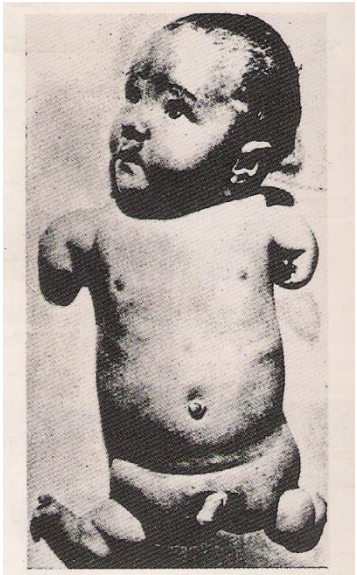
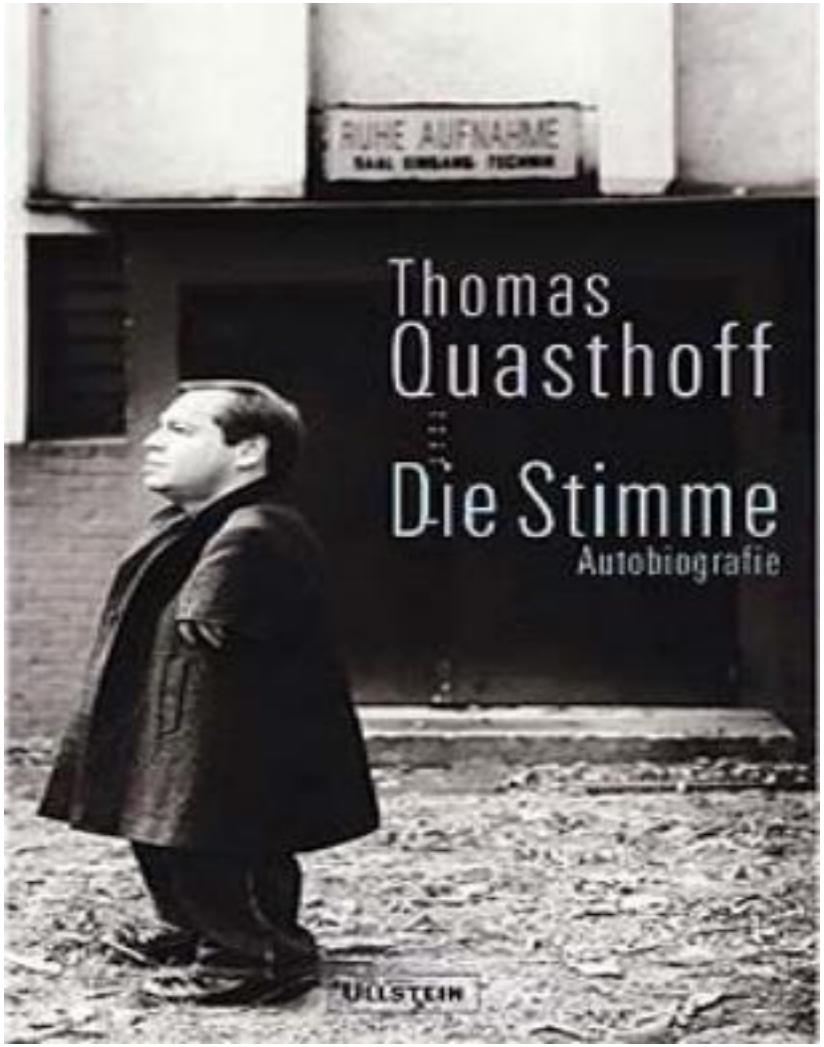
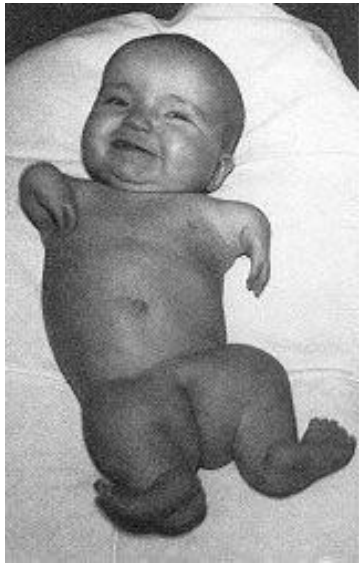
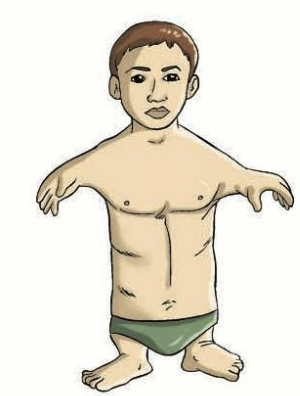


Fig.1.14: Limb abnormalities (Seal limbs) following thalidomide administration in the mother. (With courtesy of Dr. R. A. Pfeiffer from the Univ - Kinderkilinic, Munster. Direktor : Prof. Dr. H. Mai.)
Please see the text, page 39.



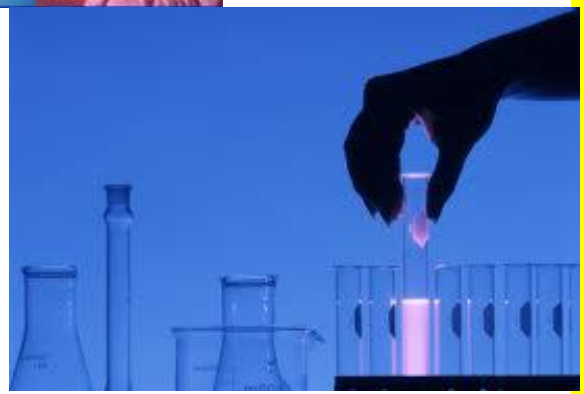




Thalidomide

- 1st introduced in 1957 – as sedative for morning sickness and nausea
- Considered as one of the most safe drug
- Thalidomide – German Pharmaceutical Company
- Marketed at least 40 Brand name- **Talimol, Nibrol, Sedimide, Softenon, Neurosedyn, Quietoplex, Contergan**
- **From 1956 to 1962, approx. 10,000 children in Africa and Europe were born with severe malformation**
- **Banned on 1962**
- New era of evolution of thalidomide started to investigate the **anti-inflammatory** and **immunomodulatory** effects of thalidomide.

Need for Translation



Research

Practice

What to do ?

What is adverse drug reaction?

- It is defined as any noxious change which is suspected to be due to a drug, occurs at doses normally used in men, requires treatment or decrease in dose or indicates caution in the future use of the drug. This definition excludes trivial or expected side effects and poisoning or overdose.

Why are ADRs Important?

They are Common

- **About 3% of all hospital admissions.**

Hospital admissions due to ADRs: 4.2-6.0% with a median of 5.8%

Pharmacoepidem & Drug Safety 6; suppl 3: s71-s77 (1997)

USA: 39 prospective studies from US hospitals

Overall incidence of serious ADRs = 6.7%
Overall incidence of fatal ADRs = 0.32%
4th - 6th leading cause of death
Increased healthcare costs

- Admission to hospital, or prolonged stay.
- Costs of treating symptoms.

Cost of drug-related morbidity and mortality >177.4 billion US$.

J Am Pharm Assoc. 41: 192(2001)

The annual cost of ADR related hospital costs **1.6-4 billion US $**

Median length of stay in hospital was 8.7 days
Total estimated cost of ADRs in Germany = 588 million $/year

Pharmacoepidemiol & Drug Safety 6; suppl 3: S79-S90 (1997)

Experience in India

- 3.7% of patients in hospital
- 0.7 % of admissions
- 1.8% fatal
- Cost Rs 187-2820, mean Rs 690 per ADR

- Ramesh et al. Pharmacoepidemiol & Drug Saf 2003

- 1.5% of admissions at Dept Gastroenterol

- Devi et al, Pharmacoepidemiol & Drug Saf 13:859 (2004)

Why are ADRs Important?

They are preventable

- Drugs which are contra-indicated or unnecessary commonly prescribed.
- Regular review of prescriptions should occur.
- Many professionals are in a position to identify them early and intervene.

Patients may not understand

- Patients may worry about unnecessarily.
- Others have ADRs and don't know it.

Why are ADRs Important?

Negative impact on patient

- Adverse effects on quality of life.
- Affects future compliance.
- Trust of health care professionals.

Classical examples of serious and unexpected adverse reactions

Medicine	Adverse reaction
Chloramphenicol	**Aplastic anaemia**
Clioquine	**Myeloptic neuropathy**
Erythromycin estolate	**Cholestatic hepatitis**
Methyldopa	**Haemolytic anaemia**
Oral Contraceptives	**Thromboembolism**
Practolol	**Sclerosing peritonitis**
Statins	**Rhabdomyolis**

Withdrawn from market

– THALIDOMIDE (1961)	Congenital limb defects
– BENOXAPROFEN (1982)	Hepatotoxicity
– PHENFORMIN (1982)	Lactic acidosis
– FENFLURAMINE (1997)	Heart-valve abnormalities
– ASTEMIZOLE (1999)	Many drug interactions
– PHENYLPROPANOLAMINE(2000)	Haemorragic stroke
– KAVA KAVA	Liver abnormalities
– CERIVASTATIN (2001)	Rhabdomyolysis
– CISAPRIDE (2000)	Cardiac arrythmias
– ROFECOXIB (2004)	Cardiovascular events
– VALDECOXIB (2005)	Cardiovascular events, serious skin reactions
– COMFREY, SENECIO	Nephrotoxicity
– TEGASEROD (2007)	Cardiovascular events
– CLOBUTINOL (2007)	Cardiac arrhythmia

Clinical trial has the following limitations:-

- Conducted in a small number of patients
- Duration of trial is usually short
- Conducted in well controlled patients avoiding the vulnerable groups (children, pregnant women, elderly patients, patients with hepatic or renal insufficiency)
- Clinical trial fails to detect:-
- Rare but serious adverse drug reactions
- Chronic toxicity of the drug
- ADR in vulnerable groups
- Information about drug interactions

Information from Post marketing

- Previously undetected adverse and beneficial effects that may be uncommon or delayed, i.e., emerging only after extended treatment
- Patterns of drug utilization
- Effect of drug overdoses
- Clinical experience with study drugs in their “natural” environment

- It is the benefit-risk profile which is more important
- It is never possible to know the whole story of a drug through clinical trials

- A clinical trial can inform the minimum information determined by the legislation and by contemporary judgments about the acceptable balance between benefit and harm

- **In fact, there is nothing that could tell you whole story of a drug**

- **How to Enhance Drug Safety ?**

- **To overcome the shortcomings of pre-marketing trial, WHO has formulated a global Pharmacovigilance Program as an important post marketing tools in ensuring the safety of pharmaceutical and related health products.**

Emphasis on

- Early warning
- Generation of knowledge
- Dissemination of information
- Rational and safe use of medicines
  - Benefit and harm together
  - The ultimate goal of this activity is to improve the safe and rational use of medicines, therapy by improving patient care and public health

What is Pharmaco-vigilance ?

Pharmaco = **Drug**

Vigilance = **To keep alert, To keep watch**

Pharmacovigilance is defined as the **science** and **activities** concerned with the **detection, assessment, understanding** and **prevention** of **adverse effects of drugs** (adverse drug reactions or ADR) or **any other drug related problem**.

(WHO, 2002)

Aims & Scope

Patient Care	• To improve patient care & safety in relation to medicines & all medical & para-medical interventions
Public Health	• To improve public health & safety in relation to the use of medicines
Risk Benefit Assessment	• To contribute to the assessment of benefit, harm, effectiveness and risk of medicines
Communication	• To promote understanding, clinical training & effective communication to health professionals & the public

- To identify new information about hazards associated with medicines
- Preventing harms to the patients
- Pharmacovigilance is related with adverse effects or any other possible drug-related problems.
- Treatment evaluation science
- "First, do no harm"
- Economical concerns
- Drug monitoring & surveillance
- Pharmacovigilance: **check if drugs on the market fulfill their intended role in society** i.e. if resources spent on drugs produce optimal results in terms of
    - *alleviation of human suffering*
    - *reduction in disease related economical loss*

- It is basically deals with-
- Collecting
- Monitoring
- Researching
- Assessing
- and evaluating

------information from health care providers and patients on the adverse effects of medication

- Presently, its concerns have been widened to include-
- • herbals
  • traditional and complementary medicines
  • blood products
  • biological
  • medical devices
  • vaccines.

Aims of Pharmacovigilance

- Improve patient care and safety in use of drugs
- Improve public health and safety in use of drugs
- Contribute to the assessment of benefit, harm, effectiveness, and risk of drugs
- Encouraging safe, rational and more effective (including cost-effective) use of drugs
- Promote understanding, education and clinical training in pharmacovigilance
- Effectively communicate to the public

-- World Health Organization

Partners

- **Government**
- Industry
- Hospitals and academia
- Medical and pharmaceutical associations
- Poison information centers
- Health professionals
- Patients
- Consumers
- Media
- WHO

Pharmacovigilance responsibilities

- Timely collection of data: recording and notification
- Appropriate assessments (data completeness, seriousness, relatedness, expectedness)
- Periodic reporting

- **What to do?**
- Collection of not only quantity reports But….QUALITY REPORTS

- **How?**
- Get more information
- Investigate at hospital level
- Help others to fill-up the ADR forms
- Keep patient's record if more information needed

Why local reports are important?

- Differ among countries in the occurrence of ADRs and other related problems
- Due to differences
  - diseases and prescribing practices
  - genetics, diet, traditions
  - drug manufacturing process
  - drug distribution and use
  - use of traditional and complementary drugs

What should be reported

- **For new drugs-**Report all suspected reactions including minor ones
- **For established or well known drugs-**All serious, unexpected, unusual ADRs
- **Change in frequency of a given reaction**
- **ADRs to generics**
- **ADRs to traditional medicines**
- **All suspected drug-drug, drug-food, drug-food supplement interactions**
- **Reactions associated with drug withdrawals**
- **ADRs due to medication errors**
- **ADRs due to lack of efficacy or suspected pharmaceutical defects**

What to report?

- All adverse events suspected to have been caused by new drugs and drugs of current interest (according to the published list of CDSCO from time to time)
- All suspected adverse drug interactions
- Reactions to any other drugs which are suspected of significantly affecting a patients management, including reactions suspected of causing :-
- * Death
- * Life threatening with real risk of dying
- * Hospitalization
- * Disability
- * Congenital anomaly
- * Required intervention to prevent permanent
- impairment or damage

Who can report?

- Any health care professional- doctors including dentist, nurses and pharmacists
- Report from any other person is not acceptable.
- **How to report?**
- The report is sent by filling up a proforma known as "Adverse Drug Event Reporting Form" for the purpose of National Pharmacovigilance Programme
- **Where to report?**
- To the same Pharmacovigilance Centre from it is collected
- OR
- To any one of the Pharmacovigilance Centre nearest to the reporter
- OR
- To the NPC at CDSCO, Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi-11011

How to assess the quality of ADR event information?

- Authenticity (including the identity of the reporter and the patient)
- Completeness of ADR reporting form
- Legibility

Causality assessment

- It is the method by which the extent of relationship between a drug and a suspected reaction is established

- Currently wide variety of causality assessment scales exist, to attribute clinical events to drugs in individual patients or in case reports, each with their own advantages and limitations.

Case causality assessment

- Did the drug cause the event?
- How close is the relationship between drug and event?

- Assessing the strength of the relationship between the drug and the event
- Can say without any doubt that a specific drug caused a specific reaction
- Use the accumulation of case reports at national level is immensely valuable providing the means for determining real cause and effect
- Use epidemiological studies to confirm causality

Causality assessment scales

- Karch & Lasagna scale
  Naranjo's scale
  WHO probability scale
  Spanish quantitative imputation scale
  Kramer's scale
  Jones scale
  European ABO system
  Bayesian system.
- **The Naranjo's scale and the WHO scale are the most commonly used scales.**

The Naranjo ADR Probability Scale

Questions	Yes	No	Don't Know
1) Are there previous conclusive reports on this reaction?	+1	0	0
2) Did the ADR appear after the suspected drug was administered?	+2	-1	0
3) Did the ADR improve when the drug was discontinued?	+1	0	0
4) Did the ADR appear with re-challenge?	+2	-1	0
5) Are there alternative causes for the ADR?	-1	+2	0
6) Did the reaction appear when placebo was given?	-1	+1	0
7) Was the drug detected in blood at toxic levels?	+1	0	0
8) Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9) Did the patient have a similar reaction to the same or similar drug in any previous exposure?	+1	0	0
10) Was the ADR confirmed by any objective evidence?	+1	0	0

The Naranjo Probability Scale

The score :-

> 8 = Highly probable

5-8 = probable

1-4 = possible

0 = doubtful

WHO Causality Categories

- C1 – Certain
- C2 – Probable
- C3 – Possible
- C4 – Unlikely
- C5 – Unclassifiable

Severity Assessment

- **Hartwig Scale**

Preventability assessment

- **Scumock & Thornton Scale**

Signal

- **Reported information on a possible causal relationship between an adverse event and a drug** the relationship being unknown or incompletely documented previously

- Usually **more than a single report** is required to generate a signal, depending upon the seriousness of the event and the quality of the information

- The publication of a signal usually implies the need for some kind of review or action

Rule for signals

- Signals should be:
  - ***S***trong
  - ***N***ew
  - ***I***mportant
  - ***P***reventable

Signal

This describes the first alert of a problem with a drug.

- By its nature a signal cannot be regarded as definitive but indicates the need for further enquiry or action.
- An alert from any available source that a drug may be associated with a previously unrecognized hazard or that a known hazard may be quantitatively (more frequent) or qualitatively (e.g., more serious) different from existing expectations
- Minimum requirement: Single, well documented report with a positive rechallenge or replication of findings in a series of reports

The SIGNAL document

- Sent to all National Centres (national distribution)
- Individualized section available to industry
- All recipients encouraged to comment on topics presented

RESTRICTED

WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database · April 2004

WHO Collaborating Centre
for International Drug Monitoring
Stora Torget 3, SE753 20 Uppsala, Sweden.
Tel +46 18 65 60 60. Fax +46 18 65 60 80
E-mail: info@who-umc.org

Signals in this issue

- Lansoprazole and severe cutaneous reactions
- Ectopic pregnancy and use of etonogestrel implants
- Reports of leukaemia and lymphoma during the use of clozapine and other atypical neuroleptics
- Leflunomide and ulcerative colitis
  Response from Aventis
- Infliximab and intestinal obstruction
- Rosiglitazone and liver toxicity

Follow-up

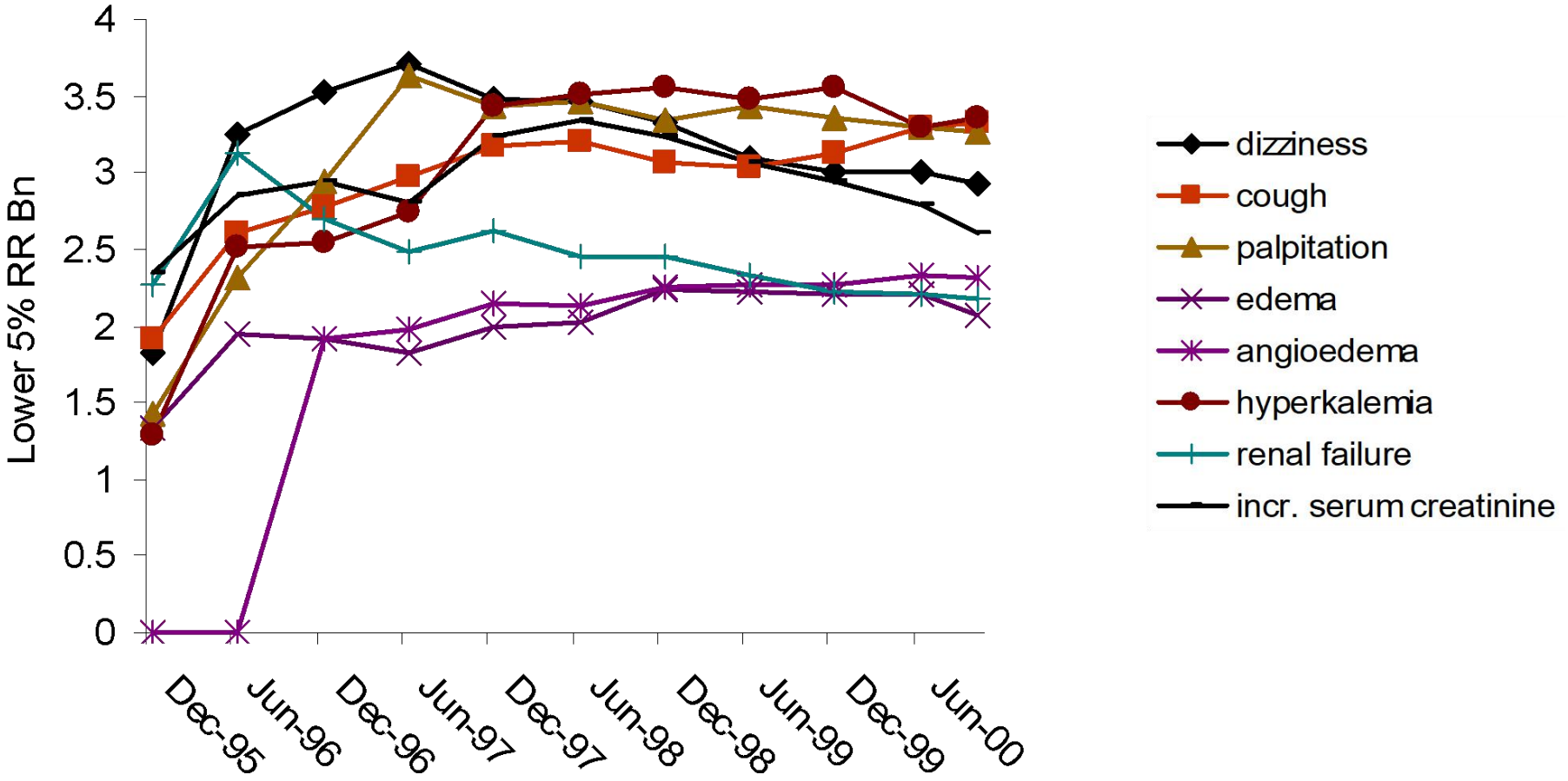
- Nelfinavir and hepatotoxicity
  Response from Pfizer and Roche
- SSRIs and gum hyperplasia
  Response from Eli Lilly and Company
- SSRIs and gum hyperplasia
  Response from Lundbeck
- Thiazolidinediones and cardiac disease
  Response from Takeda

the UPPSALA MONITORING CENTRE

All correspondence regarding signals presented in this document should go through *the* Uppsala Monitoring Centre

Accumulating Information over Time

- Lower 5% quantiles of RR stabilized fairly soon



A NEW BAYESIAN APPROACH

ADR Database - Examples of computerized databases

Data base	Location
G Practice Res Data Base	UK
Puget Sound	USA
Kaiser Permanente	USA
Medicaid	USA
Saskatchewan	Canada
Ontario Drug Benefit	Canada
Odense	Denmark
PHARMO data base	Netherlands

Vigibase

- Vigibase is the name of the WHO ADR database
- Only limited details about each suspected adverse reaction are received at the Centre.
- VigiBase™ is a unique collection of international drug safety data
- The Vigibase™ data resource is the largest and most comprehensive in the world, and is developed and maintained by the UMC on behalf of the World Health Organization.

Vigiflow

- It is web based and designed to allow for simultaneous multiple use
- It is web designed and hosted by the UMC, Sweden, Maintained centrally by UMC
- Vigiflow is a cost effective system built with a modern scalable design which ensures quality, performance and reliability with a future increasing usages

WHO Collaborating Centre for International Drug Monitoring

The Uppsala Monitoring Centre
Stora Torget 3, 75320 Uppsala, Sweden
www.who-umc.org

IMPORTANCE OF ADR REPORTING IN INDIA

- There is a rapid increase in the number of new drugs entering the market from last few decades

- India being the second most populated country has over one billion potential drug consumers, and no amount of pre-clinical and clinical data is sufficient to conclude the complete safety of a drug

IMPORTANCE OF ADR REPORTING IN INDIA

- In India, general practitioners, with an large outpatient base tend to be among the first ones to use the drugs entering the market, hence they are in the best position to assess the adverse drug reactions associated with drugs.

Limitations of Pharmacovigillence

- There is a need for a reconsideration of pharmacovigilance practice in the light of the lack of clear definition of boundaries between:
- • food,
- • medicines (including traditional medicines, herbal medicines and ‘natural products’),
- • medical devices, and
- • cosmetics.

Future challenges:*ADRs to watch*

- **Statins - ? Hepatotoxicity, Rhabdomyolysis**
- **Glitazones (Thiazolidinediones) - Hepatotoxicity, ? CCF**
- **Coxibs – CVS and ? Renal effects**
- **Newer antipsychotic drugs - Hyperglycaemia**
- **Diet drugs - (fenfluramine) valvular heart disease**

Future challenges: *ADRs to watch*

- **Sildenafil**
- **SSRIs**
- **Antiretroviral drugs**
- **Artemisinin-based combination antimalarial therapy (ACT)**
- **Herbal remedies and Nutritional supplements**

Pharmacovigilance

Summary

- Now global activity
- All kinds of drug related problems
- Acknowledged as major concern
- Laws and regulations
- Public health programmes
- Data mining, internet reporting and new data sources
- Traditional medicines
- Influencing safe prescribing and use
- Tool for Rational Drug Use

Thank you

dradhikarianjankolkata@gmail.com

☙Wish you a Happy learning !!!