Introduction to Pharmacovigilance

Medicine Safety

- To undergo treatment you have to be very healthy, because apart from your sickness you have to stand the medicine.

  Molière (Jean-Baptiste Poquelin 1622-1673)

Safe

History – Hannah Greener

- 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform before removal of an infected toenail.
- The causes of Hannah's death was investigated but it was impossible to identify what killed her. Probably she died of a lethal arrhythmia or pulmonary aspiration .
- As a result of other deaths and alerts raised by the clinicians and the public about the safety of anesthesia, *The Lancet* established a commission to take on this problem.
- The commission exhorted English doctors, including the doctor in colonies, to report deaths caused by the anesthesia.
- The results were published in The Lancet in 1893

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History - Sulfanilamide

- In 1937, there were 107 deaths in the USA, because of the use of sulfanilamide elixir, containing diethyl glycol as the solvent.
- This solvent was considered the cause of deaths, but the manufactory companies were not aware about its toxicity at that time
- Consequently, the US public health system was renovated. The Federal Food, Drug and Cosmetic Act was established in 1938;
- It mandated that the safety of drugs should be demonstrated before their market approval, and introduced the possibility of conducting factory inspections

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History - Aspirin

- In 1938, Douthwaite supposed that acetylsalicylic acid (ASA) could

cause melena .

- The studies of the gastrointestinal toxicity of ASA were inconclusive.
- However, in 1955, it was proved that ASA can cause gastrointestinal diseases
- It was contraindicated in the label for use in patients with

gastrointestinal ulcers

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History - Thalidomide

- In 1961. Dr. McBride, an Australian doctor, wrote a letter to the editor of Lancet suggesting a connection between congenital malformation of babies and thalidomide.
- In fact, he observed that the incidence of congenital malformations of babies (1.5%) had increased up to 20% in women who had taken thalidomide during pregnancy .
- At the same time, during a Pediatric Convention in Germany Dr. Lenz suggested a correlation between malformations and Thalidomide
- In 1973, a retrospective study showed the correlation between the congenital malformations and the drug
- USA,escaped the tragedy of thalidomide since US FDA had strong doubts about its safety and had not yet approved it

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Why Pharmacovigilance?

- Adverse Drug Reactions are the 4th to 6th largest cause of mortality in the USA

  (Lazarou J. et al., 1998)
- The percentage of hospital admissions due to drug related events in some countries is about or more than 10%.

- UK Study : 10.1 % (Bhalla et al, 2003)

Why pharmacovigilance?

- Tests in animals are insufficiently predictive of human safety
- The information collected during the pre-marketing phase of a medical drug is inevitably incomplete with regard to possible adverse reactions
- In clinical trials patients are selected and limited in number, the conditions of use differ from those in clinical practice and the duration of trials is limited.
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete or not available.

WHO Guidelines for setting up a PV center 2000

Drugs discontinued in UK 75-05

1975	2
1982	3
1983	3
1984	3
1985	1
1986	2
1990	2
1991	2
1992	1
1993	1
1994	1
1997	2
1998	5
1999	2
2000	3
2001	3
2004	1
2005	2

Pharmacovigilance,2nd ed, *Editors* D. Mann, Elizabeth B Andrews, Wiley 2007

Drug	Launch	Withdrawal	Reason
Phenylbutazone	1940s	1970s	bone marrow suppression
Thalidomide	1956	1962	Phocomelia
Terodiline HCl	1965	1991	Torsade de pointes
Practolol	1970	1975	Blindness, occulomucocutaneous syndrome
Nomifensine	1976	1986	Haemolytic anaemia
Benoxaprofen	1982	1982	renal & liver failure, Bone marrow depression
Terfenadine	1985	1997	Torsade de pointes
Temafloxacin	1992	1992	Haemolytic anaemia
Cisapride	1993	2000	Torsade de pointes
Cerivastatin	1997	2001	rhabdomyolysis, death
Bromfenac	1997	1998	Hepatotoxicity

Pharmacovigilance

- The science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems

Pharmacovigilance comprises

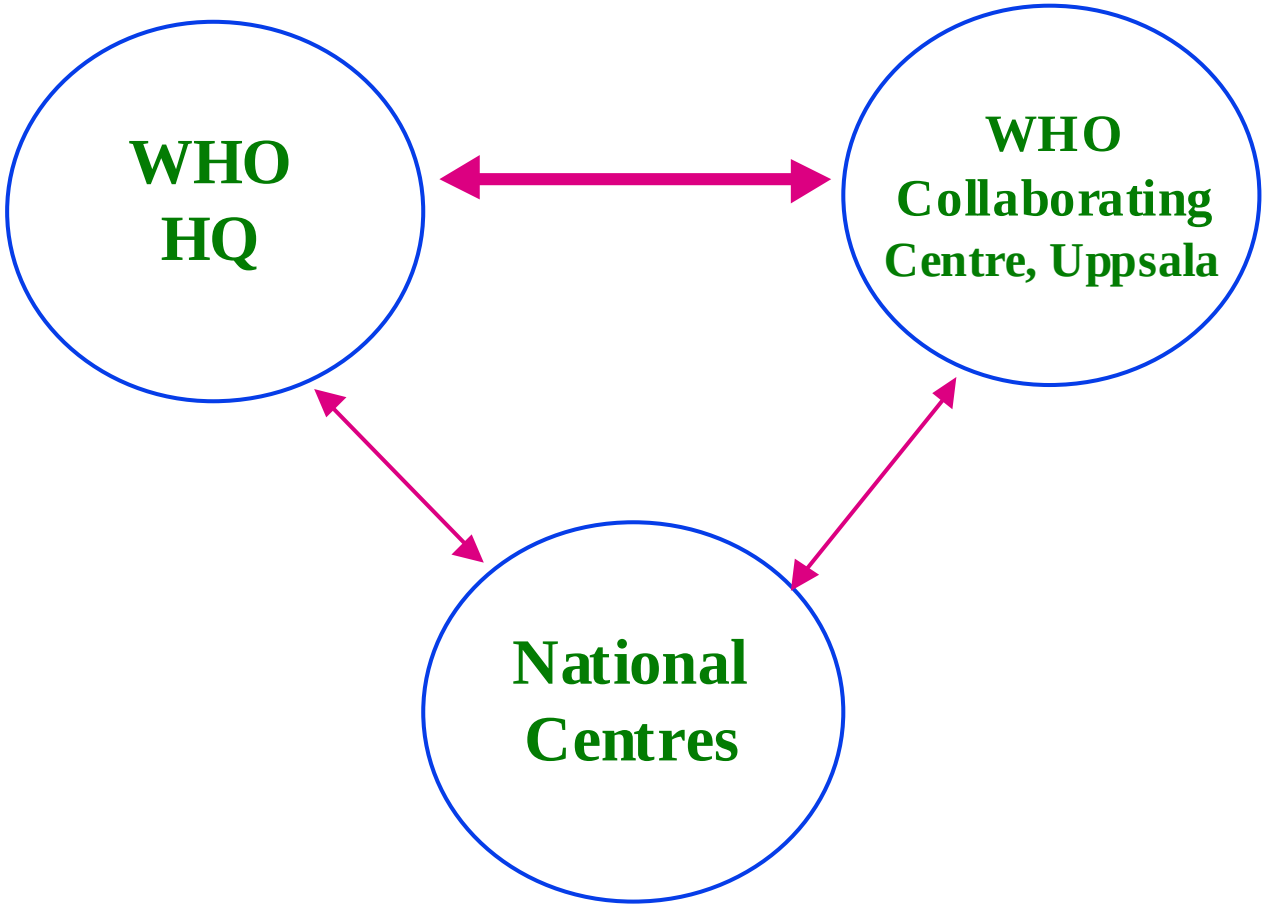
- Collecting and managing data on the safety of medicines
- Looking at the data to detect 'signals' (any new or changing safety issue)
- Evaluating the data and making decisions with regard to safety issues
- Acting to protect public health (including regulatory action)
- Communicating with stakeholders
- Audit, both of the outcomes of action taken and of the key processes involved.

http://ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm

International actions towards PV

- Since 1978, WHO international drug monitoring programme at Uppsala. It also maintains WHOART dictionary (MedDRA more accepted)
- CIOMS – Council for International Organizations of Medical Sciences is an international, nongovernmental, not-for-profit organization established jointly by WHO and UNESCO in 1949
- ICH – International Conference on Harmonization also provides guidelines on ADR reporting in E2D.
- FDA, EU, DCG(I), other country bodies all coordinate with WHO

WHO Programme for International Drug Monitoring



WHO -primary aims Pharmacovigilance

- to improve patient care and safety in relation to the use of drugs, and all medical and paramedical interventions;
- to improve public health and safety in relation to the use of drugs;
- to contribute to the assessment of benefit, harm, effectiveness and risk of drugs, encouraging their safe, rational and more effective (including cost-effective) use;
- to promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public.

WHO Programme for International Drug Monitoring (HQ)

- Policy
- Exchange of Information
- Technical support to countries
- Advisory Committee on Safety of Medicinal Products

Exchange of Information

- WHO Pharmaceuticals Newsletter
- WHO Drug Alerts
- WHO Drug Information
- WHO Restricted Pharmaceuticals List
- (Vigimed - electronic exchange)
- (Uppsala Reports)
- (Signal)

Technical support to countries

- Technical guidelines on all aspects of pharmacovigilance

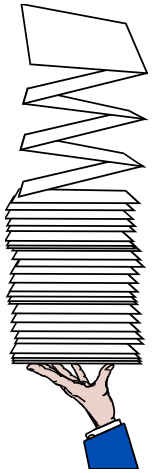
  (Several publications and documents)
- Training courses on pharmacovigilance

  (Regional Training Courses, biennial course by UMC and HQ)

WHO Collaborating Centre (Uppsala Monitoring Centre)

ADR database

- No of reports: more than 3 million
- Each year increase ~250,000 / year
- Top 5 reporting countries
  - USA
  - United Kingdom
  - Germany
  - Australia
  - Canada



WHO Collaborating Centre (Uppsala Monitoring Centre)

ADR Reports

- Analysis
- Data mining (BCPNN)
- Output
  - Feedback to National Centres
  - Signal documents
  - Ad hoc research results