Introduction to Pharmacovigilance

Module 9 Topic 1

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)

Toxic

Safe

Pharmacovigilance – What is it?

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

Pharmacovigilance – What is it?

- Vigilare = to watch
  - alert watchfulness
  - forbearance of sleep; wakefulness
  - watchfulness in respect of danger; care; caution; circumspection
  - the process of paying close and continuous attention

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.html

Why Pharmacovigilance?

- The information collected during the pre-marketing phase of a medical drug is inevitably incomplete with regard to possible adverse reactions
- Tests in animals are insufficiently predictive of human safety

Why Pharmacovigilance?

- 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

Why Pharmacovigilance?

- **Pre-marketing safety data**

Animal Experiments : Relevant?

Clinical Trials: Complete?, Covers all risks?

Adverse effects may also be missed entirely if they fail to produce clinical manifestations but are detected only by a laboratory test. One example is the case of (dex)fenfluramine associated cardiac valve abnormalities. The estimated incidence was so high that it could hardly have been missed in the clinical trials if echocardiography had been used as a routine safety assessment parameter

Why Pharmacovigilance?

Number of patients treated	Chance of missing (%)
500	95.1
1000	90.5
2500	77.9
5000	60.7
7500	47.2
10000	36.8
15000	22.3
20000	13.5
25000	8.2
30000	5.0

Why Pharmacovigilance?

- **Post-marketing Issues**

Unexpected adverse reactions

Interactions

Dependence

Long-term efficacy, Resistance

Risk factors

Quality (Counterfeit)

Cost benefit assessment

Why Pharmacovigilance?

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

(Lazarou J. et al., 1998)

Why Pharmacovigilance?

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)
- French study : 10.3 % prevalence of ADRs (Imbs et al, 1999)

Why Pharmacovigilance?

Economic impact

Drug related morbidity and mortality expenses exceeded US$ 177.4 billion in the USA in 2000

(Ernst & Grizzle, 2001)

International actions towards PV

- Since 1978, WHO international drug monitoring programme at Uppsala. 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

Drugs discontinued in UK 75-05

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

Are we catching risky medicines faster? Not Really

- The nitroimidazole- Effects & side effects
- 'No drug which is pharmacologically effective is without hazard. Furthermore, not all hazards can be known before a drug is marketed'.
- Side effects, adverse effects, toxic effects
- Type A and type B effects

Comm. for safety of drugs in UK1969,1970

Causes of ADRs

Characteristic	Type A	Type B
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from Pharmacology	Yes	Not usually
Frequency	Common	Uncommon
Overall proportion of ADRs	80%	20%
Morbidity	High	High
Mortality	Low	High
Host factors	Genetic factors may be important	Dependent on (usually uncharacterised) factors
First detection	Phases I–III	Usually phase IV,
Severity	Variable but usually mild	more severe than type A
Animal models	Usually available	Very few models

Another classification A to F

- Type A – Augmented (excess desired effect Anti diabetic, known side effect asthma beta blockers
- Type B – Bizarre anaphylaxis - idiosyncratic
- Type C – Chronic - long term exposure , dyskinesia with levodopa
- Type D – Delayed – carcinogenesis breast Ca, OC
- Type E – Post termination of therapy – antidepressants, steroids
- Type F – Failure of effect – contraceptives with rifampin, vaccines

Karen Hedenmalm. Hazards of Drug Therapy. Upsala Dissertations 2005; downloaded 2012 Jan

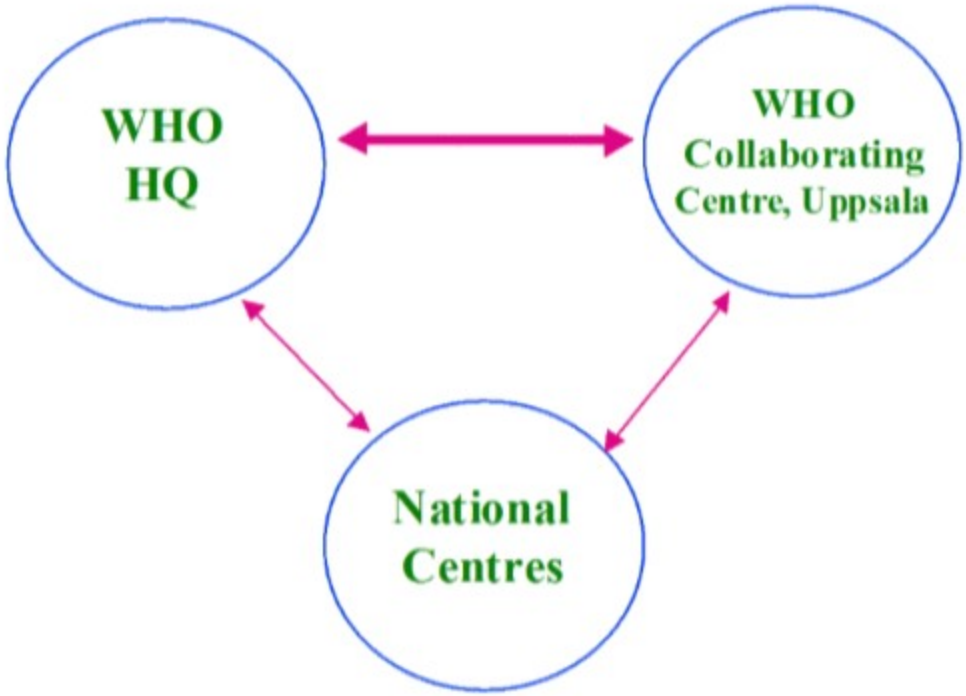
Rate of identification still same

- Many causes unknown
- Delayed toxicity will take time to manifest
- Development of new targeted drugs, use of biotechnology, peptides
- New pattern of adverse events will arise,
- e.g exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE) and blood dyscrasias with anti-tumour necrosis factor (anti-TNF) therapies or cardiovascular events with cyclo-oxygenase-II (COX-II) inhibitors may not have been reasonably expected given the known pharmacology of these agents

Regulations

- Guidelines laid down for submission of death cases, SAEs, SUSARs, spontaneous reports, annual reports, sharing info with licensee partners, etc
- Strictures penalties suggested
- Surprise audits undertaken

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;

WHO -primary aims Pharmacovigilance (contd)

- 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
- Signals

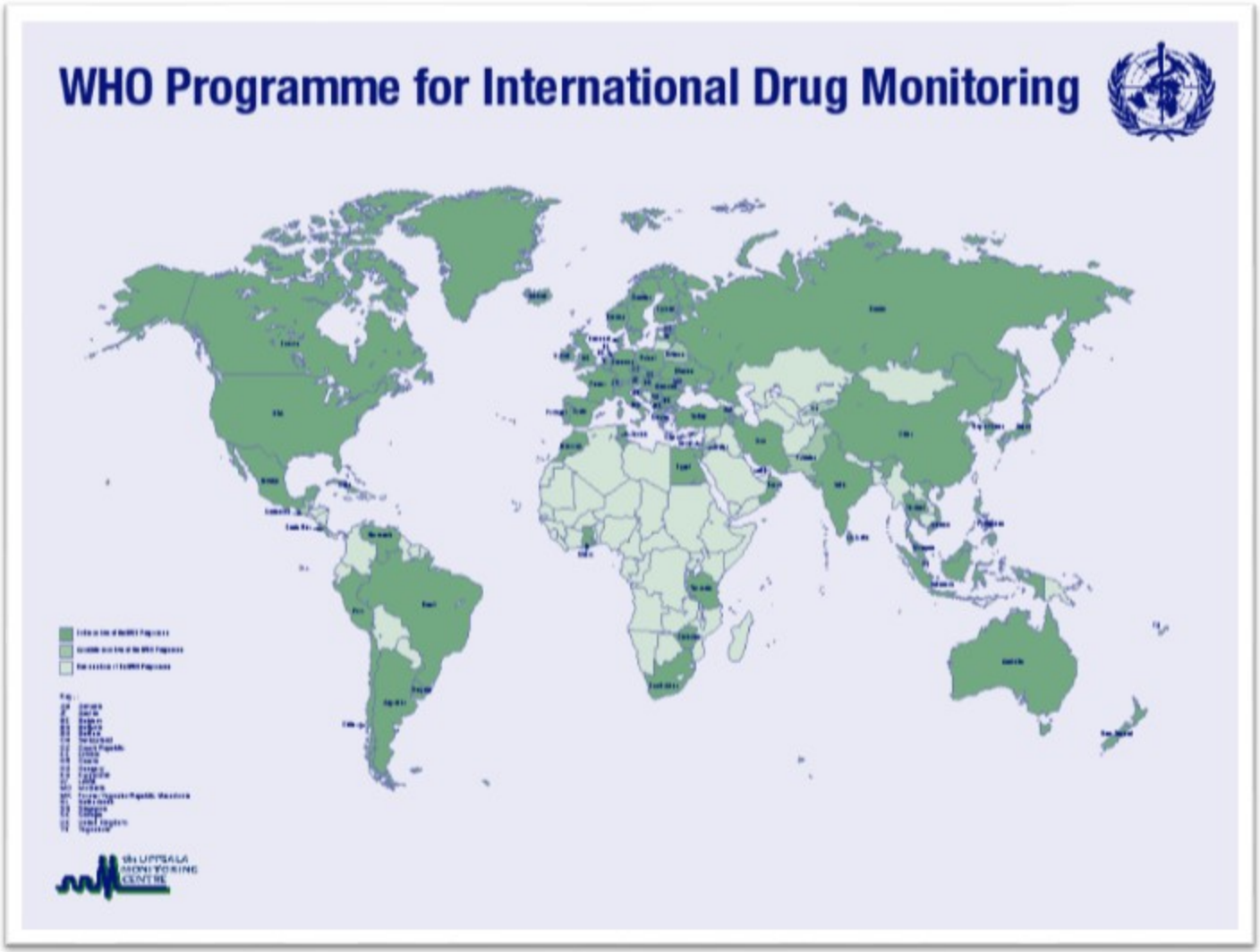
Technical support to countries

- 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 Programme for International Drug Monitoring

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

Future challenges

- Raise awareness
- Monitor all medicines
- Integrate work throughout WHO
- Improve training activities