Data Assessment in Pharmacovigilance

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Definition of pharmacovigilance
(WHO, 2002)

✓ The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem

✓ Pharmacovigilance is the same as ‘drug monitoring’
Why pharmacovigilance?

- Limited value of animal experiments in predicting human safety
- Clinical trials are limited in time and number of patients; are ‘artificial’. Patients are selected (adults, no other drugs, no other diseases). Not representative of real-life use.
- Rare or delayed serious reactions are likely to remain unnoticed
Functions of pharmacovigilance  
(WHO Guidelines, 2000)

- Detection and study of adverse reactions
- Measurement of risk
- Measurement of effectiveness
- Benefit & harm evaluation
- Dissemination of information, education

⇒ Early warning
⇒ Rational and safe use of medicines
Methods in Pharmacovigilance

- Spontaneous Reporting
- Prescription Event Monitoring
- Case Control Surveillance
- Record Linkage (automated population databases; ‘data mining’)
Formal Studies

- Defined aim, hypothesis testing (problem solving)
- Established methods (clinical trial, case control, cohort study)
- Limited as regards drugs, parameters, population (disease, number, region) and duration

Vigilance

- Open question, searching for the unexpected (‘problem raising’)
- Exploratory, controversial (SR, PEM, CCS)
- Ongoing, unrestricted (‘all’ drugs, ‘all’ patients, including subgroups)
Spontaneous Reporting

✓ Country-wide, structured system for the reporting of suspected adverse reactions to drug
Spontaneous Reporting

✓ A ‘case report’ is a notification from a practitioner regarding a patient with a disorder that is suspected to be drug-related
✓ Medical secrecy, privacy
✓ Suspicions, voluntary, confidential
Spontaneous Reporting

✓ When different doctors independently report the same unknown and unexpected adverse experiences with a drug, this can be an important signal.
What should be reported?

• Unknown, unexpected
• New drugs
• Serious (also when known)
  – Fatal, life-threatening
  – Hospitalisation
  – Persistent incapacity or disability
  – Dependence
  – Malformations
• Unexpected beneficial effects
• Unexpected ineffectiveness
Data assessment in Pharmacovigilance

1. Individual case report assessment

2. Aggregated assessment and interpretation
   - Signal detection
   - Interactions and risk factors
   - Serial (clinicopathological) study
   - Frequency estimation
Individual case report assessment

• Relevance of observation
• Coding
• Quality of documentation
• Case follow-up
• Case causality assessment
Components of a case report

- Patient
- Adverse event
- Drug exposure (suspected and other)
- Source
Patient

• Age
• Sex
• Medical history
• Case identification (confidential)
Adverse event

- **Description**: aspect, place, severity, diagnosis
- **Outcome, course, time relationship** (‘challenge, dechallenge, rechallenge’)
- **Laboratory data**
Suspected drug

- Name (product, generic, ingredients, batch no.)
- Dose, route, dates (interval, duration)
- Indication
Coding of adverse events

• Drug
  – WHO Drug Dictionary

• Adverse event
  – WHOART
  – MedDRA
  – Snomed?
Coding of adverse events

‘Reporting adverse drug reactions. Definitions of terms and criteria for their use.’

Case follow-up

- Missing data
- Laboratory data, pathology
- Outcome data (if not yet recovered)
- Underlying disease
- Verification of findings
Standardised causality assessment

- WHO system
- French system
Relevance of observation

• Unknown, unexpected, unlabeled
• Serious
• New or important drug
• Regulatory
• Scientific
• Educational
Data assessment in Pharmacovigilance

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WHO-UMC definition of a 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.

A signal consists of

- Hypothesis
- Data
- Arguments, in favor or against
Data of a signal

- Qualitative (clinical)
- Quantitative (epidemiological)
- ‘Experimental’
- Develops over time
Knowledge of adverse effect (%)
1. Signal detection
   • Selection of a possibly relevant association (hypothesis generation)
   • Preliminary assessment of the available evidence (signal strengthening)

2. Signal follow-up
<table>
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<th>Criteria for selecting a signal</th>
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- **Unknown adverse reaction**
- **Unexpected**
- **Expected but ‘unlabelled’**
- **Strong statistical connection**
- **Low background frequency**
- **Specific, characteristic**
- **Objective (definitive) event**
- **Typically drug-related event or Critical Term**
- **Serious**
- **High potential relevance**

- **Known (and labelled)**
- **Weak statistical connection**
- **High background frequency**
- **Unspecific, trivial event**
- **Subjective event**
- **Common disorder, e.g. infectious or ‘endogenous’**
- **Not serious**
- **Low relevance**
When is a signal likely to be relevant?

- **Early Warning**
  - New adverse reaction; new drug
- **Public health perspective**
  - Important drug (serious indication; widely used)
  - Serious reaction
  - Large number of cases; rapid increase in reporting
  - Regulatory intervention (prevention)
- Change in benefit/risk
- Scientific or educational value
Retrospective analysis of 107 published pharmacovigilance topics in The Netherlands


- Anaphylactic reactions 10%
- Hepatitis 13%
- Blood dyscrasias 10%
- Nervous system 16%
- Interactions 13%

Total 62%
Signal follow-up (same database)

• Drug exposure
• Development over time of the quantitative data and the consistency of the pattern
• Signal strengthening
  – individual case report assessment
  – reporting distribution
  – ‘best case-worst case’ scenario
  – targeted comparisons
  – nested case control studies
Signal follow-up (other sources)

- Similar connection in other countries
- WHO-UMC international database,
- Additional observations (e.g. literature, registration file, other databases)
- Experimental data (e.g. pharmacological, immunological)
The balance of evidence in a signal

- Quantitative strength of the association
  - number of case reports
  - statistical disproportionality
  - drug exposure

- Consistency of the data (pattern)

- Exposure-response relationship
  - site, timing, dose, reversibility

- Biological plausibility of hypothesis
  - pharmacological, pathological

- Experimental findings
  - e.g. dechallenge, rechallenge, blood levels, metabolites, drug-dependent antibodies

- Analogies

- Nature and quality of the data
  - objectivity, documentation, causality assessment
From signal to action

- Internal communication (national centres, UMC, company, academia)
- Initiation of further study (signal testing)
- Regulatory action (e.g. data sheet change)
- External communication (drug information centres, national drug bulletin, publications)
Advantages of Spontaneous Reporting

• Effective!
• Wide coverage (‘all patients, all drugs, all adverse reactions’)
• Continuous
• Rapid
• Cheap
Limitations of Spontaneous Reporting

- Suspicions
- Underreporting and bias
- Insensitive to type C adverse effects
- Drug consumption data available? (denominator)
- No quantitative assessment
- Comparison of drugs difficult
- No proof of causality

- Often further study needed (hypothesis testing, evaluation)
Signal detection

• Searching for the unexpected; ongoing
• A signal should be early and credible at the same time
• Signals may consist of only a few cases. An important signal may not be statistically prominent
• Signal testing and explanation require further study
• Many signals remain unconfirmed
  – scientific limitations
  – no funding
Standardised Case Causality Assessment

Three key questions relating to uncertainty:

• Can the drug cause the adverse reaction?
• Has the drug caused the adverse reaction?
• Will the drug cause the adverse reaction?
• MS Kramer, JM Leventhal, TA Hutchinson, et al. JAMA 1979;242:623-31
• A Emanueli, G Sacchetti. Agents Actions 1980;7:318-22
• Bégaud B, Evreux JC, Jouglard J, Lagier G. Thérapie 1985;40:111-8
• J Venulet, AG Ciucci, GC Bernecker. Int J Clin Pharmacol 1986;24:559-68
General design of systems:

- Questions
  - Sub-questions
  - Scores
- Overall score
- Causality category,
  e.g. possible, probable, etc
Four assessment criteria

• The association in time (and place) between drug administration and event
• Pharmacology (features, previous knowledge of side effects)
• Medical plausibility (characteristic signs and symptoms, laboratory tests, pathological findings)
• Likelihood or exclusion of other causes
The importance of criteria may differ for different types of reactions

- Application site reactions
- Immediate reactions
- Pharmacological effects
- Immunological reactions
- Congenital malformations
- Cancer
None of the available systems has been validated, i.e. that they consistently and reproducibly give a reasonable approximation of the truth

- Validation = ‘proving that a procedure actually leads to the expected results’
- Causality category definitions
- No gold standard
What causality assessment can do

- Decrease disagreement between assessors
- Classify relationship likelihood (semi-quantitative)
- Mark individual case reports
- Education / improvement of scientific assessment

What causality assessment cannot do

- Exact quantitative measurement of relationship likelihood
- Distinguish valid from invalid cases
- Prove the connection between drug and event
- Quantify the contribution of a drug to the development of an adverse event
- Change uncertainty into certainty
WHO Causality Categories
(All points should be reasonably complied with)

Certain

- Event or laboratory test abnormality with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (An objective and specific medical disorder or recognised pharmacological phenomenon)
- Rechallenge (if necessary)

*Drug Safety 1994;10:93-102*
Probable
• Event or laboratory test abnormality with reasonable time relationship to drug intake
• Unlikely to be attributed to disease or other drugs
• Response to withdrawal clinically reasonable
• Rechallenge not necessary

Possible
• Event or laboratory test abnormality with reasonable time relationship to drug intake
• Could also be explained by disease or other drugs
• Information on drug withdrawal lacking or unclear
Unlikely
• Event or laboratory test abnormality with a time relationship to drug intake that makes a connection improbable (but not impossible)
• Diseases or other drugs provide plausible explanations

Conditional / Unclassified
• Event or laboratory test abnormality
• More data for proper assessment needed
• Or additional data under examination
Specific etiologic-diagnostic systems

• Disease definition (including other forms)
• Clinical appearance and pathology
• Signs of severity
• Aetiology (various possible causes) and diagnosis
• Evidence implicating a drug
• Chronological criteria
• Management

Questions for the future

• Causality assessment as a routine of all reports, or only in selected cases?

• One general system, or special systems adapted to specific adverse reactions?
Signal management (1)

- Selection of the relevant data (case reports) and delineation of the signal (hypothesis)
- Literature search
- Survey of available data and identification of missing data and unanswered questions
- Gathering of missing data (follow-up of cases; structured enquiry)
- Consultation with the WHO Uppsala Monitoring Centre
- Contact between National Centre and company; study of the data in the registration file
Signal management (2)

- (Re)assessment of all available data
- Writing a report, containing:
  - summary of the signal
  - presentation of original data
  - presentation of additional information
  - discussion, with reference to positive and negative arguments
  - hypothesis (preliminary conclusion)
  - suggestions for further study

This report may serve as a basis for decision-making by the regulator and the pharmaceutical company, for communication between national centres, and for the preparation of information for practitioners and in the published literature.
Pharmacovigilance can only be effective through the active participation of practitioners!!