Introduction to Pharmacoepidemiology

Pharmacovigilance

2012 Mid-Year ISPE Meeting
Miami, April 21-23, 2012

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Conflict of Interest Declaration

• The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the Université de Montréal or the Government of Canada.
• No other conflict of interest to declare.

Pharmacovigilance Definition

Science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem [env]

• Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and

• Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

EMA 2012 Guideline on good pharmacovigilence practice (GVP)
Important Concepts in Pharmacovigilance

**Adverse Event (AE)**
Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

**Adverse (Drug) Reaction (ADR)**
A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

**Causal relationship**
A relationship between two phenomena or events (A and B) in which A precedes and causes B. In pharmacovigilance, a medicine causing an adverse reaction.

Classification of ADRs

- **Type A**: Augmentation or exaggerated and dose-related response (e.g., Digoxin toxicity, NSAIDs induced Lithium toxicity)
- **Type B**: Bizarre and unpredictable (e.g., Anaphylaxis & Penicillin, Aplastic Anemia & Clozapine)
- **Type C**: Chronic or long-term related (e.g., Drug tolerance; Withdrawal effects)
- **Type D**: Delayed (e.g., Cancer; Birth Defects)

Historical Perspective

**International Drug Monitoring**

- 1961 The supposedly “safe” sleeping thalidomide pill disaster
- 1962 Request from the World Health Assembly to the WHO General Director to study ways to make drugs safer
- 1967 The development of an ‘International System’ was initiated (20th World Health Assembly)
- 1968 First country members: Australia, Canada, Germany, Netherlands, New Zealand, Sweden, UK, and U.S.A.
  - Pilot results (30,000 case reports / 12 countries)
  - Reporting standards
  - Adverse reaction terminology
  - List of all drugs reported
  - Signal reports are regularly distributed to participant members
Clinical Trials: “Gold standard methodology” to study safety of drugs?

“Regardless of improvements that we may see in the area of measuring adverse effects, we think that regulatory agencies, authors of compendia, practicing physicians, and the general public must better appreciate the limitations of what can be learned about medication-related harms from randomized trials and other studies. Case reports and observational studies will remain essential for identifying late appearing and uncommon serious adverse events”

Ioannidis JP, Mulrow CD and Goodman SN. Editorial Annals Internal Medicine, 21 February 2006

Pharmacovigilance - Context

...the study of the safety of marketed drugs under the practical conditions of clinical use in large communities

Data Elements for Transmission of ICSRs
ICH Guideline E2B(R2)

Administrative Information: Country, report ID, type and date of report, source(s) of information, sender, etc.

Case Information: Patient, age, weight, height, sex, relevant medical history & concurrent conditions

Reaction(s)/Event(s): Description, start & end reaction date, exposure-reaction interval and duration, lab tests & procedures, outcome (autopsy if fatal)?

Drug(s) information (both suspect and concomitant medications): Name, batch/lot #, indication, dosage & route of administration, start date, duration, action taken, rechallenge (and effect)?

Sender or Reporter Comments

ADR Reporting Time Frames
Expedited Reporting (ICH-E2A)

- Fatal or Life-Threatening Unexpected ADRs: ...ASAP but no later than 7d after first knowledge by the sponsor
- Serious and/or Unexpected ADRs: ...ASAP but no later than 15d after
- ...all other (PSUR)

Minimum criteria for reporting (for regulatory purposes)

- Identifiable patient;
- Suspect medicinal product;
- Identifiable reporting source;
- Event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

Imputability (Causality Assessment)

1. Global Introspection (e.g., WHO)
2. Algorithms (e.g., RUCAM)
3. Bayesian probabilities
"...In practice few adverse reactions are 'certain' or 'unlikely', most are somewhere in between these extremes, i.e. 'possible' or 'probable'. In an attempt to solve this problem many systems have been developed for a structured and harmonised assessment of causality. None of these systems, however, have been shown to produce a precise and reliable quantitative estimation of relationship likelihood."

### Analysis of ADR Databases

**The Challenges (1)**

**Inherent to Pharmacovigilance**

- Multiple medications and/or medical conditions
- More than one event per report
- No benefits of research (randomization, control, etc.)
- Causality is usually not possible to determine
Analysis of ADR Databases
The Challenges (2)

Reporting Related Practices
- Under-reporting
- Prompt to biases (publicity, litigation, etc.)
- Operational changes (reporting, coding, prescribing, etc.)

Analysis of ADR Databases
The Challenges (3)

Data Related

Quality & Completeness
- Follow-up (delayed reactions)
- Exposure time-event window
- Exposure dose-event relationship

Adverse event incidence
- low ADR vs high AE (background) incidence
- low drug exposure data

No denominator (population at risk)
The Pigeonhole File System (1966)

Upon receipt, the reports are acknowledged and filed in a "pigeonhole" file. Coloured markers are attached to reports of severe and unusual reactions; those reactions that resolved when the drug was discontinued and reappeared when the patient was rechallenged with the drug; reports of fetal abnormalities suspected of being due to a drug administered during pregnancy; and reports of deaths associated with the administration of a drug. This system of coloured markers facilitates surveillance of the files and provides an early alert to developing trends.

SIGNAL – CIOMS VIII (2010)

"Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory and, when necessary, remedial actions."

Characteristics of Signals

- Are working hypothesis
- May point to unknown adverse reaction associations for:
  - Old or new drugs
  - Drug-drug or other type of interactions
  - General or restricted group populations
- Are not by themselves proof of causal relationship
- Require always further evaluation
- May or may not lead to specific market interventions

Adapted from Hauben & Aronson. Drug Safety 2009
**Approaches for Signal Detection from ADR Databases**

**TRADITIONAL**
- Manual review of all incoming reports by PV staff
- Structured review of PV studies (PEM)
- Crude frequency counts and/or reporting rates

**AUTOMATED**
- Automatic / Periodic screening of ADR-DB (PEM & SRS)
  - Data Mining Algorithms (DMA): e.g.; PRR [UK], BCPNN [WHO], EBGM [FDA]
  - Pattern recognition & Graphical display of "outliers" (PEM & SRS)

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**CIOMS VIII Signal Management Process**

- Individual Case AE Report
  - SD in SRS
  - Traditional PV
  - DMA
  - Triage of Outputs (PV Intelligence)
  - Signal Evaluation
  - Impact? Prioritization?
    - Yes → Further Investigation?
    - No → Routine Monitoring
  - Other Safety Data

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**Future ADR Data Sources?**

- Spontaneous Reporting Systems
- Administrative / Claims / Other Databases

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“...Automated signal detection (and DMAs) can be applied to observational studies, drug utilisation studies and clinical trials.”

Shahid, JAW Drug Safety, 2007, 10, 7, 615-606
“Time and again there has been confusion, for regulators, companies or the media, following from the uncertain nature of signals generated by spontaneous reporting and the inherent limitations of the system to produce secure and quantitative information. Spontaneous reporting has been designed as a system for hypothesis generation in the first place. As a rule, further study, using the most appropriate (and usually different) method, is needed to put the hypothesis to the test.”

Meyboon et al. 2002

Post-Market Surveillance & Risk Management
(Regulatory Perspective)

Signal Assessment

Risk Assessment

Signal Detection / Selection

Risk Mitigation / Strategies Developed

Risk Minimisation

Muchas Gracias!

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