Pharmacovigilance and Risk Management

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with thanks to prof. M. Bogaert
“Pharmacovigilance”

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

(WHO definition)
Pharmacovigilance and risk management

- After the thalidomide disaster
- Why is pharmacovigilance necessary?
- Methods in pharmacovigilance
- Risk management
- Conclusions
- Some important references
After the thalidomide disaster

Thalidomide and congenital abnormalities
Mc Bride WG.: Lancet 1961;2:1358

In this Letter to the editor, the Australian physician McBride reports that he had noted an increased frequency of limb malformations (“phocomelia”) among babies, and that a common denominator seemed to be the intake of a new hypnotic drug – thalidomide – by their mothers.
After the thalidomide disaster

• In the wake of the thalidomide disaster (± 10,000 children with severe malformations), governments in several countries set up procedures for a systematic collection of information about adverse drug reactions: the first pharmacovigilance centres.
  – Based on the spontaneous reporting of adverse drug reactions by physicians.
  – First organized in e.g. the Netherlands, Sweden, U.K., U.S.A., New-Zealand, West-Germany.
After the thalidomide disaster

• In 1968, 10 countries agreed to pool their data in a WHO sponsored international drug monitoring project.

• July 2007: 83 countries participate in the “WHO-programme for international drug monitoring”.

• In Belgium, the pharmacovigilance centre was set up in 1976.

• Since 1995, a European pharmacovigilance system is operational. Since 2001, there is a legal basis for the obligations for pharmacovigilance for the national pharmacovigilance centres and the drug companies (directive 2001/83/EC).

• With directive 2004/27/EC, pharmacovigilance becomes more proactive: “risk-management” strategy.
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When a drug goes to market, we know everything about its safety.

Wrong.

FDA MedWatch
If it’s serious, we need to know.
Why is pharmacovigilance necessary?

Limitations of clinical trials performed before drug approval (phase I-, II-, III-trials)

- “too few”: on average 1,500 patients
- “too simple”: selected population
- “too median-aged”: not too young, not too old
- “too narrow”: well-defined indications
- “too brief”: exposure and follow-up
# Statistical Considerations

<table>
<thead>
<tr>
<th>Incidence (risk) of ADR to be detected</th>
<th>Spontaneous background incidence of the adverse event</th>
<th>Minimum number of patients to be exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 in 100</td>
<td>0</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>1 in 10 000</td>
<td>520</td>
</tr>
<tr>
<td></td>
<td>1 in 1 000</td>
<td>730</td>
</tr>
<tr>
<td></td>
<td>1 in 100</td>
<td>2 000</td>
</tr>
<tr>
<td>1 in 500</td>
<td>0</td>
<td>1 800</td>
</tr>
<tr>
<td></td>
<td>1 in 10 000</td>
<td>3 200</td>
</tr>
<tr>
<td></td>
<td>1 in 1 000</td>
<td>6 700</td>
</tr>
<tr>
<td></td>
<td>1 in 100</td>
<td>35 900</td>
</tr>
<tr>
<td>1 in 1000</td>
<td>0</td>
<td>3 600</td>
</tr>
<tr>
<td></td>
<td>1 in 10 000</td>
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<td>1 in 1 000</td>
<td>20 300</td>
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<td></td>
<td>1 in 100</td>
<td>136 400</td>
</tr>
<tr>
<td>1 in 5000</td>
<td>0</td>
<td>18 200</td>
</tr>
<tr>
<td></td>
<td>1 in 10 000</td>
<td>67 400</td>
</tr>
<tr>
<td></td>
<td>1 in 1 000</td>
<td>363 000</td>
</tr>
<tr>
<td></td>
<td>1 in 100</td>
<td>3 255 000</td>
</tr>
</tbody>
</table>

*Table 1.1 From Committee on Safety of Medicines Report on the Second Working Party on Adverse Reactions*
Why is pharmacovigilance necessary?

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Methods in pharmacovigilance

- Randomized trials
- Observational data
Methods in pharmacovigilance: randomized trials

Rarely performed within the scope of pharmacovigilance because:

- no “real-life” situation
- ethical objections to perform a randomized trial.
- limitations in duration of trial and in number of patients.

But …. evidence of a causal association is high when an increased risk is found
Example of a randomized trial, important for pharmacovigilance

- Rofecoxib: the APPROVe-trial

In September 2004, the company decides to withdraw Vioxx® and VioxxDolor®, containing the COX-2-selective non-steroidal anti-inflammatory drug rofecoxib.

Reason for withdrawal: the APPROVe-trial (*Adenomatous polyp prevention on Vioxx*), showing a higher incidence of major cardiovascular events (myocardial infarction, cerebrovascular accident) in patients taking rofecoxib, compared to patients taking placebo.
Methods in pharmacovigilance

- Randomized trials
- Observational data
Methods in pharmacovigilance: observational data

- Case-reports in the literature
- Spontaneous reporting systems
- Epidemiological study designs (e.g. cohort-studies, case-control studies)
Spontaneous reporting systems

Health professionals can report suspected adverse drug reactions to:

- the health authorities.
  
  In Belgium, this is the “Belgian Centre for Pharmacovigilance”. The “yellow cards” are sent regularly with the national drug bulletin “Folia Pharmacotherapeutica” and the national drug formulary “Gecommentarieerd Geneesmiddelenrepertorium”. Recently an electronic form is developed, more details via Folia Pharmacotherapeutica october 2006 (www.bcfi.be or www.cbip.be).
- the marketing authorization holder.
**RAPPORT CONFIDENTIEL DE REACTION INDESIRABLE AUX MEDICAMENTS**

1. **PATIENT**
   - **Initials:**
   - **Age:** < 2 ans: date de naissance.../...
   - **Poids:**... kg
   - **Sexe:** M/F
   - **Medicament(s) administré(s):**
     - durant la grossesse ☐
     - pendant l'allaitement ☐

2. **REACTION INDESIRABLE**
   - Nature et intensité (notion de gravité) de la réaction:

3. **MEDICAMENT(S)**
   - Nom (surligner les médicaments suspects)
   - posologie par 24h
   - Voie d'administration
   - Dates d'administration
   - Indications
   - Nbre de prises
   - Dose unitaire
   - Début
   - Fin

4. **EVOLUTION**
   - Guérison sans séquelle ☐
   - Guérison avec séquelle(s) ☐
   - Date:...
   - Amélioration en cours ☐
   - Pas d'amélioration ☐
   - Inconnue ☐
   - Décès ☐
   - Date:...

5. **AUTRE(S) OBSERVATION(S)**
   - Autre(s) maladie(s):
   - Allergie(s) connue(s):
   - Tabagisme
   - Alcoolisme

6. **Divers:**
   - Cachet du rapporteur
   - Date:...
   - Signature

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**OUI - NON**

Y a-t-il eu réadministration du ou des médicament(s) suspecté(s)?

Si OUI,y a-t-il eu réapparition de la réaction indésirable?
### 1. PATIENT

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Leeftijd: indien &lt; 2 jaar: geboortedatum ....../....</td>
<td>- gedurende zwangerschap o .... maanden</td>
<td>Genzog zonder restletsel o</td>
<td></td>
</tr>
<tr>
<td>Gewicht: ...... kg</td>
<td>- gedurende lactatie o</td>
<td>Genzog met restletsel(s) o</td>
<td></td>
</tr>
</tbody>
</table>

### 2. BIJWERKING

Aard en ernst:

Begindatum: ....../.... Einddatum: ....../.... Hospitalisatie: JA - NEEN

Resultaten van laboratoriumtests of andere onderzoeken (bij hepatitis, uitsluiten van virale hepatitis)

### 3. GENEESMIDDELEN

<table>
<thead>
<tr>
<th>Naam (verdachte geneesmiddelen onderlijnen)</th>
<th>posologie per 24u</th>
<th>Toedienings-weg</th>
<th>Toedienings-data</th>
<th>Indicaties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aant. innamen</td>
<td>Eenhedsdosis</td>
<td>Begin</td>
<td>Einde</td>
<td></td>
</tr>
</tbody>
</table>

### 5. ANDERE BEVINDINGEN

Andere ziekten:

Gekende allergie:

Alcoholmisbruik O Tabakmisbruik O

### Varia:

Stempel of naam, adres en telefoonnummer

### Was er hertoediening van het verdacht geneesmiddel? JA - NEEN

Indien JA, trad de bijwerking terug op? JA - NEEN

Handtekening: ....../....
Spontaneous reporting systems

Strengths
• Inexpensive and simple to operate
• Covers all drugs and the whole patient population
• Does not interfere with prescribing habits.

Weaknesses
- Clinical information often too limited to permit a thorough case evaluation
- Problem of under-reporting
- Not possible to calculate absolute risk
- Problem of causality assessment.
Spontaneous reporting systems

Number of patients with ADR

\[
\text{Absolute risk} = \frac{\text{Number of patients with ADR}}{\text{Number of exposed patients}}
\]

but…

- Number of patients with ADR not known (underreporting)
- Number of exposed patients not known (estimation of sales data and prescription statistics)
Spontaneous reporting systems

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- Problem of causality assessment.
Spontaneous reporting systems

Problem of causality assessment in individual case-reports, due to

- Co-morbidity
- Intake of other drugs
- The fact that symptoms suggesting a side effect, sometimes occur with a high background incidence.
Spontaneous reporting systems: discussion

- Spontaneous reporting systems are primarily designed to detect early drug safety signals, thus creating “hypotheses”.
- Some examples.
  - Glafenine and anaphylactic shock
  - Anorexigens and pulmonary hypertension
  - Oseltamivir and psychiatric symptoms
  - Rofecoxib and myocardial infarction

P.S. recently (august 11, 2007): lumiracoxib and serious liver toxicity
Spontaneous reporting systems: discussion

- But,
  - How to find the needle in the haystack?
  - How many reports for a signal?
  - How many reports for an alert?

- A lot of “hypotheses” or even “signals” remain unverified and unevaluated.
- On the other hand, regulatory actions are sometimes taken in the absence of evidence on frequency of the adverse reaction or on patients especially at risk.
Spontaneous reporting systems: discussion

- Feed back to health professionals is very important. In Belgium, the Belgian Centre for Pharmacotherapeutic Information tries to do this in collaboration with the Belgian Centre for Pharmacovigilance.
- Spontaneous reporting systems have an important role in increasing the awareness of potential problems associated with drugs.
Which suspected adverse drug reactions should be reported?  
(Folia Pharmacotherapeutica october 2006)

- Suspected adverse reactions not mentioned in SPC or literature (or not mentioned at the observed frequency or seriousness).
- Suspected adverse reactions with recently commercialised drugs.
- Serious suspected adverse reactions (i.e. life threatening, resulting in or prolonging hospitalisation, leading to persistent incapacity, congenital malformations...).
- Suspected adverse reactions in children.
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Risk management

Set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions.

As defined in the “Guideline on risk management systems for medicinal products for human use”, CHMP, EMEA (2005)
Risk management

- The marketing authorization holder submits a “risk management plan” to the health authority.
- The “risk management plan” should already be part of the application dossier for most drugs (e.g. new active substances).
- A “risk management plan” can however be necessary at any time point after commercialization, when a safety concern has emerged.
Risk management

-The need for a more pro-active approach, as planned in the “risk management plan”, is increasing as
  - the pressure to shorten approval-times increases;
  - after approval, there is a robust marketing, and rapidly thousands, even million patients are exposed to the new drug;
  - more « potent » drugs become available.
Risk management

The « risk management plan » must include the following information.

- The risk profile of the drug (at that time point).
- The pharmacovigilance activities that are planned.
  - only the routine activities (spontaneous reporting, «Periodic Safety Update Reports»)?
  - or also additional activities?
    - clinical trials or epidemiological studies (e.g. drug or disease registries, cohort studies….)
  - need for « risk minimisation activities »?
Risk management: « risk minimisation activities »

• Provision of information and education, e.g.
  • via SPC / patient leaflet
  • additional educational material (cfr. isotretinoin-containing drugs).

• Restrictions of the use of the medicine, e.g.
  • control of legal status, e.g. only to be prescribed in hospital or by specialists
  • control of prescription size or validity
  • restricted access programmes.
But…
- So far there is no legal basis requiring that drug companies complete the data collection as specified in the risk management plan.
- There is a need for efficient, independent evaluation methods of the risk minimization activities.
- There is a need for more transparency on the “risk management plans” adopted.
- Not all risks are foreseeable, and risk management plans will not replace, but rather complement the procedures currently used to detect safety signals!
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Conclusions

- The need to monitor the safety of a drug after its commercialization shall always be necessary.
- Each method has its advantages and its disadvantages, and should be complementary.
- There is an urgent call for pharmacovigilance activities receiving public, non-“drug company” funding, with research driven and guided by independent bodies.
- The role of the health professional is of the utmost importance for pharmacovigilance to succeed.

As Dr. Mc Bride ended his Letter to the Lancet: “Have any of your readers seen similar abnormalities …?”
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- Viewpoint. Watching for safer medicines: part 1 and part 2

- Pharmacovigilance in focus. A selection of reprinted articles concerning the theory and practice of pharmacovigilance. *Drug Safety* (Reprint Collection 2001 ISSN: 0114-5916)

• European legislation
  Regulation (EC) No 726/2004
  http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm
• ICH Topic E 2 E: Note for guidance on planning pharmacovigilance activities (CPMP/ICH/5716/03): via www.emea.europa.eu