Improving PharmacoVigilance in the European Union

Experiences from Stockholm, Sweden

Ulf Bergman
Ulf Bergman, MD, PhD

Regional Adverse Drug Reaction Unit
Department of Clinical Pharmacology
Karolinska Institutet,
Karolinska University Hospital,
Stockholm, Sweden
Ulf Bergman

ulf.bergman@karolinska.se

Conflict of interest statement
No conflicts of interest of relevance for this presentation
Outline:

- historical background of ADR
- to describe how we have integrated the regulatory task of pharmacovigilance for the Swedish Medical Products Agency
- with the public health focus on drug safety for the Stockholm County council - the local health care provider
The European Union with 27 countries (+3 associates) with 490 million people
Six Health Care Regions - each with a medical school and with a Department of Clinical Pharmacology

Northern Region
Umeå

Uppsala Region
Uppsala

Western Region
Gothenburg

Southern Region
Lund and Malmö

Stockholm Region
Stockholm

South-east Region
Linköping
Stockholm county council

1.9 million inhabitants

7 Emergency hospitals

Karolinska University Hospital with two sites: Huddinge and Solna
Functions of Clinical Pharmacology
(WHO 1970)

“To improve patient care by promoting the safer and more effective use of drugs; to increase knowledge through research; to pass on knowledge through teaching; and to provide services, such as drug information, drug analysis, the monitoring of drug abuse, and advice on the experimental design of clinical drug studies.

All these functions should in fact serve to enhance benefit-cost ratios of drugs.”
Department of Clinical Pharmacology at Karolinska Institutet- Karolinska University Hospital

Right drug for the
Right patient in the
Right dose for the
Right time to the
Right costs
Clinical Pharmacology

- Therapeutic Drug Monitoring
- Drug Information Centre
- Drug & Therapeutics Committee
- Regional Adverse Drug Reactions Unit
- Pharmacoepidemiology

and much much more
Pharmacovigilance from a regulatory and from a public health point of view
Take Home messages:

*From a regulatory point of view:*
submit an ADR report

*From a public health point of view:*
Recognize Adverse Drug Reactions - a Differential diagnosis

An ADR diagnosis: (a minimum an ICD-10)

Y 57.9 *Unintended effect of a medication in therapeutic use*
History of Pharmacovigilance

Surveillance of Adverse Drug Reactions - ADRs

Thalidomide
THALIDOMIDE AND CONGENITAL ABNORMALITIES

Sir, - Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide (“Distaval”) during pregnancy, as an antiemetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme – i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?


In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. Referring to “reports from two overseas sources possibly associating thalidomide (“Distaval”) with harmful effects on the foetus in early pregnancy”. Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide. – ED.L.
Dear Doctor, may we introduce another form for you to fill in?
Voluntary reporting of suspected ADRs in Sweden since 1965
The main purpose with the spontaneous reporting system is to detect new ADRs unknown at the time of marketing.
This serves as a signalling system generating hypothesis that generally have to be tested in pharmacoepidemiological studies.
Since 1968

WHO

collects voluntary reports of

Adverse Drug Reactions

from 10 countries
WHO drug monitoring programme

Participating countries 1968
What is an adverse drug reaction?

ADR

A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function

WHO, 1972
Pharmacovigilance: monitoring and analysis of spontaneous adverse drug reactions - ADRs
Since 1978

WHO-CC the UMC

Uppsala Monitoring Centre

collects voluntary reports of
Adverse Drug Reactions
from all over the world
Member countries 1968-2008
WHO Collaborating Centre for International Drug Monitoring - The Uppsala Monitoring Centre > 4 million reports
Cumulative number of active reports processed per year
WHO

WHO Collaborating Centre for International Drug Monitoring
40th Anniversary

The Uppsala Monitoring Centre
30th Anniversary in October 2008
David Finney (92) & Barbro Westerholm (75) at the Anniversary of the WHO UMC in Uppsala in October 2008
David Finney  
The scientific group on monitoring adverse drug reactions reported to the Director General, WHO 1964
"After 50 years of unsuccessful attempts to find new and more effective treatment approaches . . . our results lend support to the use of thalidomide in the initial treatment of elderly patients with multiple myeloma."

See Articles, page 13.
Pharmacovigilance from a regulatory point of view
Medical Products Agency, Uppsala
SWEDIS

Swedish Drug Information System
From 1965-2007

105,000 causality assessed ADR reports
National spontaneous ADRs from all Health Care in Sweden
Number of reports - 13 yrs

- 1994: 3000
- 1995: 3000
- 1996: 3000
- 1997: 3000
- 1998: 3000
- 1999: 3000
- 2000: 3000
- 2001: 3000
- 2002: 3000
- 2003: 3000
- 2004: 3000
- 2005: 3000
- 2006: 5130

Legend:
- 500
- 1000
- 1500
- 2000
- 2500
- 3000
- 3500
- 4000
- 4500
Decentralised ADR reporting

North Region
Umeå
1992

Uppsala Region
Uppsala
1996

Western Region
Göteborg
1997

Southern Region
Lund och Malmö
1996

Stockholm Region
Stockholm
1995

Southwestern Region
Linköping
2000
ADR reporting in France

- 31 regional centers receive spontaneous reports from the health care
- Common database since 1984
- Coordinated by Afssaps, (‘Agence Française de Sécurité Sanitaire des Produits de Santé’)

Assignments for centres:
- collect, evaluate and stimulate ADR reporting
- inform and co-operate with the health care profession
- expert, consultant questionnaires epidemiological studies
- support scientific development
ADR reporting in UK

5 regional centres "Yellow Card Centres"
1. Yellow Card Centre Northern and Yorkshire
2. Yellow Card Centre West Midlands
3. Yellow Card Centre Mersey
4. Yellow Card Centre Wales
5. Yellow Card Centre Scotland

Common database "Yellow Card database"
These centres ska focus on:
follow-up, education and communication
to stimulate ADR reporting
Medication Safety in the European Union

Regional Adverse Drug Reaction Unit in Stockholm in the Department of Clinical Pharmacology Karolinska Institutet, Karolinska University Hospital
Regional ADR Unit in Stockholm

1000 ADR reports/year
Causality Assessment

Known reaction
Time-relationship
Disappear at Dechallenge
Re-appear at Rechallenge
Cannot be explained by other medications
Cannot be explained by the underlying diseases
Do you remember which symptoms you began with, and which are side effects?
Weekly meeting with the Regional ADR Unit
Number of ADR reports per year in Stockholm
Causality Assessment

1000 ADR reports/year corresponds to 529 ADR reports per million inhabitants

a figure well above the highest in Europe (450 ADRs per million, Frauenhofer ISI 2005).
Figur 1. Utdrag från kommissionens rapport: Antal rapporter per miljon invånare (Fraunhofer ISI 2005)
Don't get the impression that I'm knocked out!!!
This is in fact the starting position ........
Medical Products Agency, Uppsala
Number of ADR reports per year in Stockholm

![Graph showing the number of ADR reports per year in Stockholm from 2000 to 2007. The graph depicts the total number of reports and the number of reports for AB-län (private) and I-län (industry).]
The Adverse Drug Reactions head for Uppsala
The European Union with 27 countries (+3 associates) with 490 million people
ADR reports in Sweden 2000-2007

Total reports in Sweden from 2000 to 2007.
Reports of serious adverse drug reactions are transferred to the EudraVigilance database.
Medication Safety in the European Union

Reports are sent electronically.

All regulatory authorities have access to the system designed to perform signal detection and analyses.
Serious suspected adverse drug reactions are collected centrally in the European pharmacovigilance database EudraVigilance - created in 2001.
The EudraVigilance system
2008 > 1 million reports
Pharmacovigilance within Europe is co-ordinated by the EMEA in London.

Its Committee for Human Medicinal Products – CHMP – gives scientific opinions about pre- and marketed products.

Much is also delegated to the Pharmacovigilance working party.
PRESS RELEASE

The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia

The European Medicines Agency (EMEA) has recommended the suspension of the marketing authorisation for Acomplia (rimonabant) from Sanofi-Aventis. The EMEA’s Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Acomplia no longer outweigh its risks and the marketing authorisation should be suspended across the European Union (EU).

Acomplia has been authorised in the EU since June 2006 as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors. Warnings about psychiatric side effects, in particular depression, have been included in the product information since Acomplia was first authorised. The product information for Acomplia has been continuously updated and strengthened to include further contraindications and upgraded warnings on these concerns to
Pharmacovigilance from a public health point of view
Epidemiology of ADRs
ADRs:

Type A
augmented pharmacological effects

Type B
bizzare effects
Types of ADRs

Type A

Predictable from pharmacology of the drug, dose-dependent and preventable

Type B

Bizzare, unpredictable from known pharmacology, and no dose-dependency
Fokusrapport

Läkemedelsbiverkningar som orsak till inläggning på sjukhus

Stockholms läns landsting

2005
Swedish ADR hospitalization studies


**ADR hospitalizations in %**


Mean AGE in ADR hospitalizations


Number of drugs/patient with ADR hospitalizations

% phararamacological (typ A) ADRs


Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients.

British Medical Journal 2004;329;15-9

Types of ADRs

Type A
Predictable from pharmacology of the drug, dose-dependent and preventable
95%

Type B
Bizzare, unpredictable from known pharmacology, and no dose-dependency
5%

How Many ADRs Were Avoidable?

Definitely avoidable  8.6%
Possibly avoidable  63.1%
Not avoidable  28.1%

72 % of ADRs were definitely or possibly avoidable

Importance for

Health care provider

Industry and Regulatory Agency

Type A

Type B

Adverse Drug Reactions
The Swedish Medical Quality Council 1999
Swedish Medical Quality Council

Focus on type A reactions from a public health point of view

Reporting of clinically important ADRs should be stimulated by providing feedback to each clinic

Reporting of Type-A reactions should be considered as a quality indicator to be commented upon in a “quality report”.

Feedback of ADR reporting

We tested this in field study in 4 clinics:
2 Internal Medicine, Cardiology, Psychiatry
## Internal Medicine, Halmstad

<table>
<thead>
<tr>
<th>Year</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of reports</td>
<td>11</td>
<td>8</td>
<td>17</td>
<td>23</td>
<td>28</td>
<td>100</td>
<td>271</td>
</tr>
</tbody>
</table>
Acceptance of this Quality Indicator with ADR feed-back was tested by a VAS (10 best) (Visual Analog Scale)
Do you think presenting the reported side effects will help improve the quality of drug usage?

n=52  Mean=79
Do you regard the reported side effects of type A to be a valuable indicator of quality in the reporting of side effects? n=52  Mean=70
Will the presentation of number of reported side effects from your clinic, affect your reporting of side effects in the future? affect your motivation to report side effects in the future?

n=52  Mean=74
Primary Health Care centres (PHC) in Stockholm were offered contracts where the PHCs received extra payment depending on the adherence to the proposed guidelines.

The contract required each practice to analyse their prescribing and to write a “quality report” including questions about adverse events and reporting.

The project budget was €2 Mio and the savings was estimated to be 5 times more: 10 Mio
In the annual “quality report”, among the 139 PHCs participating in the program:

80% stated that they discussed ADRs as part of their internal continuous professional education

50% stated that they had local routines for ADR reporting

An estimated 300 reports were submitted from these PHCs, cf 585 received from primary care the same year
In agreement with these positive experiences, the Regional Drug Safety Centre is now providing feedback of ADRs to all seven emergency hospitals in Stockholm.
Number of ADR reports per year in Stockholm

TOTALEN AB+I LÄN

![Graph showing the number of ADR reports per year in Stockholm from 2000 to 2007. The x-axis represents the years 2000 to 2007, and the y-axis represents the number of reports ranging from 0 to 1200. The graph displays the total number of reports, with a breakdown between AB-län and I-län. The data shows a general increase in reports from 2000 to 2007.](image-url)
In agreement with these positive experiences, the Regional Drug Safety Centre is now providing feedback of ADRs to all seven emergency hospitals in Stockholm.

In 2006, 529 ADR reports per million inhabitants were received at the Centre, a figure well above the highest in Europe (450 ADRs per million, Frauenhofer ISI 2005).
Assessment of the European Community System of Pharmacovigilance (Fraunhofer 2006.) Reports per million inhabitants

Figur 1. Utdrag från kommissionens rapport: Antal rapporter per miljon invånare (Fraunhofer ISI 2005)
An ADR diagnosis:
(a minimum an ICD-10)

Y 57.9

Unintended effect of a medication in therapeutic use
Number of hospitalizations with the ADR diagnosis in Stockholm

Individer och vårdtillfällen med orsaksdiagnos Y57.9 i SLL
### Number of hospitalizations with the ADR diagnosis in Stockholm

#### Andelen vårdtillfällen i SLL med Y57.9 diagnos

<table>
<thead>
<tr>
<th>År</th>
<th>vårdtillfällen SLL</th>
<th>vårdtillfällen Y57.9</th>
<th>% av vårdtillf med Y57.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>276930</td>
<td>295</td>
<td>0,11%</td>
</tr>
<tr>
<td>2001</td>
<td>278390</td>
<td>340</td>
<td>0,12%</td>
</tr>
<tr>
<td>2002</td>
<td>286572</td>
<td>434</td>
<td>0,15%</td>
</tr>
<tr>
<td>2003</td>
<td>291626</td>
<td>463</td>
<td>0,16%</td>
</tr>
<tr>
<td>2004</td>
<td>294072</td>
<td>512</td>
<td>0,17%</td>
</tr>
<tr>
<td>2005</td>
<td>298138</td>
<td>527</td>
<td>0,18%</td>
</tr>
<tr>
<td>2006</td>
<td>303552</td>
<td>543</td>
<td>0,18%</td>
</tr>
<tr>
<td>2007</td>
<td>307515</td>
<td>647</td>
<td>0,21%</td>
</tr>
</tbody>
</table>
Don't get the impression that I'm knocked out!!!
This is in fact the starting position ........
Pharmacovigilance from a regulatory point of view: voluntary reporting

Public health point of view: diagnosis of ADRs
Keep in mind the origin

- Advancement in safety heavily relies on reporting of safety events by health care professionals.
Take Home messages:

From a regulatory point of view:
submit an ADR report

From a public health point of view:
Recognize Adverse Drug Reactions - a Differential diagnosis

An ADR diagnosis: (a minimum an ICD-10)

Y 57.9 Unintended effect of a medication in therapeutic use
Thank you for staying till the end!
Time for
Questions & Answeres?

If you don’t ask stupid question
You remain stupid

Alvan Feinstein
ICPE Conference

25th Anniversary 2009
Mid-Year Meeting
– April 25-27, 2009
– Stockholm, Sweden

Annual Meeting
– August 16-19, 2009
– Providence, Rhode Island, USA
Welcome to Stockholm! 25th ICPE
Mid-Year Meeting   April 25-27   2009
Conclusion

Feedback and economic incentives of ADR reporting seem to be powerful tools in enhancing the awareness of ADRs and thus the quality of drug prescribing.

Integrating adverse events into a drug-prescribing program may result in better understanding of benefits and risks of drug treatment in individual patients.
Medication Safety in the European Union

Pharmaceutical companies are also required to provide regulators with annual safety reports from clinical trials and periodic safety update reports at regular intervals post-authorisation.