Signal Detection in Spontaneous Reports

Congreso de Farmacovigilancia, León, 2010

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What is a "signal"?

• Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.
Why signal?

- Improved usage of the drug
- More benefit, less harm to patients

What should be achieved?

- Signals should not be missed
- Signals should be found early
- 'False' signals should be kept to a minimum
Steps in Signal Detection

• report collection
• (database cleaning)
• quantitative assessment
• qualitative assessment
• (communication)
• (evaluation)

Spontaneous reports

• Advantages:
  - wide coverage of medicines
  - no exclusion criteria
  - no time limits
  - reflect real life use of medicines
  - reflect real life concerns (of prescribers / consumers)
Spontaneous reports

- Disadvantages:
  - data quality
    - accuracy of diagnosis
    - confounding factors
  - generalisability (e.g., hospital patients?)
  - comparability across drugs
  - lack of numerator (under-reporting)
  - lack of denominator (drug utilisation data)
  - duplication
  - delayed reporting

Single report assessment

- There may be weeks, months, or even years between receipt of the reports
- Many different people may be involved in report processing and review
- Important to collect as much relevant information as possible with the initial report
Single report assessment

• What are the important pieces of information?
  - information about the medicine
  - information about the patient
  - information about the reaction

Information about the medicine(s)

• Dates of use
• Indication
• Dosage
• Route of administration
Information about the patient

• Demographics (age, sex)
• Other diseases (past or present)
• Allergies?
• Weight?
• Smoking status?

Information about the reaction(s)

• Description
  – including, for example, laboratory tests
• Timing
• Response to dechallenge or rechallenge
Timing

- Many reactions have a characteristic time interval:
  - anaphylaxis
  - alopecia
  - solid organ cancer

Indication for use

- Many drugs have multiple indications
- It may be important to differentiate them:
  - anticonvulsants (epilepsy / pain)
  - opioids (what's the cause of the pain?)
  - chemotherapy (location of tumour?)
Assessing causality

- Causality can be considered at the level of a single report or multiple reports

- Single report: what is the range of possible causes and can they be reliably excluded?

- Multiple reports: looking for patterns in the data

Quantitative

- Automated procedures:
  - disproportionality assessment
  - triage
Relative reporting rates

- Key to signal detection in spontaneous reports
- What is reported more often than expected (from a comparator)?
- Comparator can be whole database, other drugs in the same class, or a single drug
- Can be automated
- Can screen large amounts of data

Relative reporting rates

- Essential process reduces to a 2x2 table
- Based on the comparator
  - expected rate = c/d*b
  - observed number = a
  - how do these compare?

<table>
<thead>
<tr>
<th>Reports of ADR</th>
<th>Total reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>a</td>
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<tr>
<td>Comparator</td>
<td>c</td>
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</tbody>
</table>
### Statistical measures

- Many different statistical measures of disproportionality
  - PRR (proportional reporting ratio); ROR (reporting odds ratio); EBGM; IC (information component – used at UMC)
- All based on the same data (ie, any method can be used on a given database of ADR reports)
- All give broadly similar results

### IC example

<table>
<thead>
<tr>
<th>Date</th>
<th>2010-05-05</th>
<th>Number of combinations in recall</th>
<th>1</th>
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<tr>
<td>Total number of reports</td>
<td>4,905,533</td>
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</table>
IC calculation

<table>
<thead>
<tr>
<th></th>
<th>nausea</th>
<th>all reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluvoxamine</td>
<td>1200</td>
<td>7365</td>
</tr>
<tr>
<td>all drugs</td>
<td>214,193</td>
<td>4,680,915</td>
</tr>
</tbody>
</table>

- 4.6% of all reports describe nausea
- 16.3% of fluvoxamine reports describe nausea
- Nausea 3.6 times as often reported with fluvoxamine
- RR = 3.6
- IC = 1.83 \((-\log_2 3.6)\)
- IC_{95} = 1.75 = lower 95% credibility bound of the IC

Measures of disproportionality

<table>
<thead>
<tr>
<th></th>
<th>specific reaction</th>
<th>all reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>specific drug</td>
<td>(N_{comb})</td>
<td>(N_{drug})</td>
</tr>
<tr>
<td>all drugs</td>
<td>(N_{adr})</td>
<td>(N_{tot})</td>
</tr>
</tbody>
</table>

- observed = \(N_{comb}\)
- expected = \(N_{adr}/N_{tot} \times N_{drug}\)

- IC = \(\log_2((N_{comb}+0.5)/(N_{adr}/N_{tot} \times N_{drug} + 0.5))\)
- PRR = \((N_{comb}/N_{drug})/(N_{adr}/N_{tot})\)
- ROR = \((N_{comb}/(N_{drug}-N_{comb}))/(N_{adr}/(N_{tot}-N_{adr}))\)
Relative reporting rates

- Reporting rate for ADR is higher for drug A than for comparator
- Does this mean the incidence of ADR is higher for drug A than for comparator?
- Factors to consider:
  - what's the appropriate comparator?
  - what increases reporting of that drug-ADR pair?
  - what decreases reporting of other drug-ADR pairs?
  - (overall reporting rate for each drug shouldn't matter)

Relative reporting rates

- Appropriate comparator:
  - ideally, a drug used in a similar population
  - decrease effects of disease, age, etc
- Factors that influence reporting rate:
  - (length of time drug has been on the market)
  - publicity
  - special reporting programs
- What about under-reporting?
Example - cerivastatin

<table>
<thead>
<tr>
<th></th>
<th>rhabdomyolysis (observed)</th>
<th>all reports</th>
<th>rhabdomyolysis (expected)</th>
<th>observed / expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerivastatin</td>
<td>5326</td>
<td>14044</td>
<td>43</td>
<td>123</td>
</tr>
<tr>
<td>simvastatin</td>
<td>2519</td>
<td>31774</td>
<td>98</td>
<td>26</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>1374</td>
<td>28286</td>
<td>87</td>
<td>16</td>
</tr>
<tr>
<td>whole database</td>
<td>15044</td>
<td>4888246</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cerivastatin

- The reporting of rhabdomyolysis is increased for all statins compared to the database as a whole
  - what's the significance of this?
  - what's the risk-benefit assessment?
- The reporting of rhabdomyolysis is greater for cerivastatin than for other statins
  - same indication?
  - similar population?
  - similar benefits?
UMC signal process

• VigiBase overview
• Triage
• Internal (UMC) review
• External (expert panel) review

How many combinations?

• 1 combination = 1 drug + 1 reaction

• 5,639,680 reports in Vigibase (Sept 2010)
• 976,948 unique combinations (using WHO-ART)
• 1,486,764 unique combinations (using MedDRA)
• ~150,000 unique combinations per quarter
Triage

UMC triage rules:
• $I_C_{025} > 0$
• Reports from >1 country
• One of the following:
  – significantly increasing IC (at least one unit since last quarter)
  – new drug (up to 5 years in DD) and serious reaction (WHO-ART critical term)

Triage

• Other triage rules:
  – targeted medical events (events likely to be drug-related:
    severe cutaneous adverse reactions, anaphylaxis,
    agranulocytosis)
  – specific medicines (malaria, TB, HIV)
  – new drugs widely used
**Internal review**

- ~600 combinations ("potential signals") from triages
- Reviewed by UMC signal team:
  - is it known / expected?
  - is it disease-related?
  - is it due to other drugs?
  - are there duplicate reports?
  - are the reports informative/good quality?

**Sources of information:**
- labelling (SPC, PDR)
- drug information (Martindale, DrugDex)
- medical textbook
- Medline

**Signal team decides need for further review:**
- internal (UMC)
- external (expert review panel)
UMC review panel

- 51 experts (volunteers) from around the world
- Doctors and pharmacists
- Specific areas of interest
  - drug(s) or reaction(s)
  - includes herbals, vaccines, congenital malformations

Signal assessment

- Recent data from drug-ADR combinations reviewed at UMC:
  - 40-50% already known / labelled
  - 10-20% due to disease being treated
  - 5% due to concomitant disease
Other factors

- Is it new information?
- Are there public health considerations?
- Is it preventable?

New information

- Signal definition refers to "incompletely documented" relationships between drug and event
- This may include:
  - estimation of frequency
  - details of severity
  - time course of event
  - risk factors / at risk groups
Public health impact

- Is this a severe or sustained event?
- How many people are at risk?
  - information on drug usage

Preventability

- Can the risk be reduced?
  - labelling
  - communication
  - restricted access
  - laboratory testing
  - dose reduction
Keep in mind...

• Spontaneous reports reflect the beliefs and concerns of the reporters
• In addition to new signals, reports may also indicate areas where there is:
  - lack of adequate information
  - inappropriate use of medicines

Conclusion

• Signal detection requires a combination of automated clinical approaches
• Statistical methods don’t remove the need to understand:
  - the natural history of the disease under treatment
  - the background incidence of the reaction
  - the public health context
References

• Measures of disproportionality:

• Triage:

Thank you!