Summary of content

- What is a signal?
- Recognising a signal
- What can be achieved by you?
- Clinical assessment of individual events
- Clinical review of collated events
- Principles of signal detection
- Ta
Definition 1

A signal refers to ‘reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously’.

WHO
Definition 2

- In practice it means, a strong suspicion of an adverse reaction that has not been recognised previously.
Recognising a signal
Signal identification

- Record
- Collate
- Look!!
Recognition of a signal 1

How do we know when events are not recognised reactions?

- *Martindale*
- *DrugDex*
- *Physicians Desk Reference* (PDR).

All available on website of Micromedex Healthcare Series www.thomsonhc.com
Recognition of a signal 2

- You don’t need to do data mining (BCPNN), or proportional reporting ratios (PRR), or disproportionality analysis to identify signals.
- Careful clinical assessment of your own events data is the quickest and most satisfying way.

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Recognition of a signal 3

- Routine clinical appraisal facilitates the earliest possible generation of hypotheses
- Automated signal detection
  - good for testing hypotheses
  - identifying missed signals
  - still needs clinical confirmation
Recognition of a signal 4

Clinical review the quickest method
- careful
- informed
- systematic
- standardised
- clinical review
- In your centre
What can be achieved – by you?
What can be achieved?

Example: IMMP - omeprazole

- Hyponatremia
- Dry mouth
- Taste disturbance
- Interstitial nephritis
- Polydypsia / polyuria
- Polymyositis
Omeprazole

- Hepatitis
- Angioedema / urticaria
- Bone marrow depression
- Carcinoid tumour
- Gastric polyps
- Diarrhoea
Omeprazole

- Hallucinations
- Amnesia / confusion
- Headache
- Myalgia
- Gynaecomastia / galactorrhoea

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Omeprazole

- Paraesthesia
- Pruritus
- Rash
- Extrapyramidal symptoms
- Blood dyscrasias
Clinical assessment of individual events
COX-2 inhibitors and disturbance of vision

EXAMPLE 1
Example 1

- M 78
- Shoulder pain
- Rofecoxib 50 mg once
- Woke next morning with
  - no vision right eye
  - 6/18 left eye
- Recovered next day
Example 1

- M 81
- Osteoarthritis knee
- Celecoxib 100mg daily
- Central loss of vision
- Onset after each morning dose, recovering after a few hours
- No recurrence after withdrawal
Example 1

- These 2 case reports can be called the INDEX CASES
- Contain good information
  - close time relationship
  - positive dechallenge
  - one had rechallenge
Now we look for information that may strengthen the signal:

- Other case reports
- WHO database (Vigibase)
- Literature
- Mechanism
### Example 1

**Other reports of eye problems - blurred vision**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rof</td>
<td>M 58</td>
<td>?</td>
</tr>
<tr>
<td>Cel</td>
<td>F 53</td>
<td>200mg</td>
</tr>
<tr>
<td>Cel</td>
<td>F 59</td>
<td>200mg</td>
</tr>
<tr>
<td>Cel</td>
<td>F71</td>
<td>200</td>
</tr>
</tbody>
</table>

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Example 1

WHO reports

- **Celecoxib**
  - Blindness 12
  - Temporary blindness 4
  - Vision abnormal 181

- **Rofecoxib**
  - Blindness 22
  - Temporary blindness 5
  - Vision abnormal 167
Example 1

**Literature search**

- One case report with celecoxib
  - Orange spots in both visual fields. (Lund & Neiman, 2001)
- No reports with rofecoxib
- Visual field defects have been reported rarely with the traditional NSAIDs
Example 1
Mechanism

- Interference with retinal blood flow by inhibition of prostaglandins and related substances.
Example 1

Conclusion

- Two good index cases
- Several supporting cases
- Supporting cases in WHO database
- Similar reports for related drugs
- A plausible mechanism
- Only one similar report in the literature
- We have a signal!
Clinical review of collated events
COX-2 inhibitors and prothrombotic disorders

EXAMPLE 2
Demo

- Cluster of events
Profile of Incidents - Celecoxib and Rofecoxib

n=131                 n=71

Chart shows the incidence of adverse events associated with Celecoxib and Rofecoxib.

- Celecoxib
- Rofecoxib

System Organ Class

- Accidents
- Alimentary
- Autonomic
- Circulatory
- Endocrine/Metabolic
- ENT
- Eyes
- Haematological
- Hepatobiliary
- Immunological
- Infectious
- Musculo-skeletal
- Neoplasms
- Neurological
- Psychiatric
- Respiratory
- Skin
- Urogenital

The bar chart indicates the percentage of total incidents for each system organ class.
Prothrombotic events

Summary of findings

- No difference in rates of IHD / stroke between rofecoxib & celecoxib
- Higher rate of prothrombotic events than comparators
- Shorter time to onset of death than comparators
- Differences in death rates due to prothrombotic events
- Higher rate of cardiac dysrythmias with celecoxib
Principles of signal detection
Remember

- Treatment dates - starting date & ending
- Date of onset of event
- Was the patient on the drug when the event began?
- Calculate onset time
- Effect of dechallenge / rechallenge
Signal assessment

Other questions

- Could the problems be caused by a disease?
  - The disease being treated
  - A co-morbid condition
- Could the problems be caused by another drug?
- Are the events caused by related drugs?
- Is it relevant or important?
Look for non-random features

- Gender
- Age
- Duration to onset
  - Survival / life table analysis
Non-random features

- Differences in means
  - Patients with reaction vs patients in cohort
  - t-test
- Differences in rates
  - RR with CI
- Survival or life table analysis
  - Clustering around a certain duration
  - Differences between medicines
- Multiple logistic regression
Collate reports clinically

- By Clinical Category (CC)
- Then in clinically related groups
  - Anatomical functional change
    - Clinical sub-group
      - Primary event term
      - Secondary event term

- Motto:

  Sort & see & pursue

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Identifying early signals

Report your signals to:

- your advisory committee &/or regulatory authority
- local health practitioners
- the Uppsala Monitoring Centre
- local ADR bulletin
- medical journal
Signal identification

- Record
- Collate
- Look!!
Thank You