Identifying early signals

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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

• An early signal, when there is not strong evidence, can be called an ALERT
Recognition of a signal 1

• How do we know when events are not recognised reactions?
• A standard method is to refer to *Martindale* and the *Physicians Desk Reference* (PDR). If the events suspected of being an adverse reaction are not in these references, then they can be regarded as a signal. (UMC)
Recognition of a signal 2
clinical review the quickest method

- careful
- informed
- systematic
- standardised
- clinical review
- at point of collection
Recognition of a signal 3

• Routine clinical appraisal of reports
  – facilitates the earliest possible generation of hypotheses

• Automated signal detection
  – good for testing hypotheses
  – identifying missed signals
  » still needs clinical confirmation
Example 1:
COX-2 inhibitors and disturbance of vision

- 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: COX-2 inhibitors and disturbance of vision

- 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:
COX-2 inhibitors and disturbance of vision

• These 2 case reports can be called the INDEX CASES
• Contain good information
  – close time relationship
  – positive dechallenge
  – one had rechallenge
Example 1: COX-2 inhibitors and disturbance of vision

Now we look for information that may strengthen this alert:

• Other case reports
• WHO database
• 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>
Example 1:
Relevant reports in WHO database

• 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!
Example 2:
Sumatriptan & pain activation

• F 43 6mg subcutaneous
• Hysterectomy 2 weeks previously
• severe aggravation of pain for 1 hour

• Kicked by horse 1 month previously
• severe aggravation of pain
Example 2:
Sumatriptan & pain activation

- F 47 6mg subcutaneous
- Sunburn
- Pain aggravated for 30 minutes

- M 59 6mg subcutaneous
- Cuts on hands fishing same day
- Extreme pain 2 hours
Example 2:
Sumatriptan & pain activation

- F 52 6mg subcutaneous
- Fracture humerus
- Aggravation of pain for 2 hours
- Recurred 3 times with rechallenge for 4 weeks after fracture
Example 2: Sumatriptan & pain activation

M 51  6mg subcutaneous
Rheumatoid arthritis
Severe aggravation of pain with every use
Duration: 24 - 48 hours
Example 2:
Sumatriptan & pain activation

F 37 6mg subcutaneous

Colitis flared up within 5 minutes

Duration: 10 days
Example 2: Sumatriptan & pain activation

F 34 6mg subcutaneous
Severe sacro-iliac pain
Used twice with recurrence
Duration: “all day”
Example 2:
Sumatriptan & pain activation

F 34   6mg subcutaneous
Causes toothache
Duration: 1 hour

F ?   6mg subcutaneous
Causes painful ears
Duration: 15 minutes
Example 2: Sumatriptan & pain activation

Mechanism

Sumatriptan is an agonist at $5HT_1$ receptors

5HT is involved with:

- pain sensitising at inflammatory sites
- pain processing in the spinal cord
Example 2: Sumatriptan & pain activation

Conclusion 1

- 10 case reports
- Plausible time relationship
- Positive dechallenges
- Positive rechallenges
- Plausible mechanism
- Nothing in WHO or literature
Example 2: Sumatriptan & pain activation

Conclusion 2

• Two types of reaction
  – pain trauma activated
  – pain inflammation activated

• New terms

• We have a strong signal!
Example 3:
Interaction of celecoxib & amitriptyline 1

- Patient: F 60
- On regular amitriptyline
- Nausea every time celecoxib taken with amitriptyline 10 mg nocte
- Celecoxib 100mg bd
- Celecoxib inhibits P450 2D6
- Amitriptyline metabolised by P450 2D6
Example 3:
Interaction of celecoxib & amitriptyline 2

- Patient: F 45
- Long term amitriptyline
- 3 days after celecoxib 200mg
  - rapid runs of SVT
  - ceased within 24 hours of stopping celecoxib
Example 3

Interaction 3: WHO data

- F 70 tachycardia onset 1 day + amitriptyline
- F 48 palpitations onset 1 month + celecoxib
- F 33 tachycardia, chest pain, dyspnoea
  - 1 day + celecoxib
- F 61 Palpitation, tremor, diarrhoea
  - 1 day + celecoxib
Example 3

Interaction 4: conclusion

- Two good index cases
- Supporting cases in WHO
- Nothing in the literature
- Plausible mechanism
- Nothing in Martindale or PDR
- We have a signal!
Signal assessment

Other questions

• Could the problems be caused by a disease?
• Could the problems be caused by another drug?
• Are the events caused by related drugs?
• Is it relevant or important?
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