From a single case to a case series

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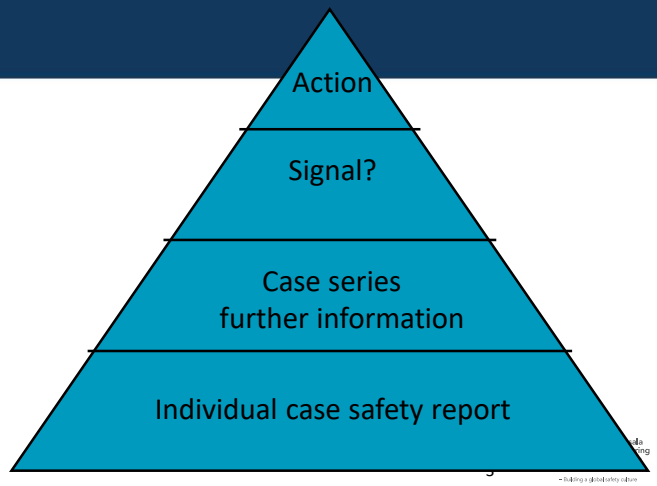
Aims of Causality Assessment

To define the relationship between a drug and an ADR:

- did the drug cause this clinical condition?
- does the drug increase the risk of this clinical condition?

To support signal detectionand risk minimizing action by basing it mon evidence



What is a Case Series in our signal detection process?

A group of reports on patients with similar exposure (drug) and experiencing a similar suspected ADR

Assessing a case series may supply additional information that is missing in individual case reports

Single case causality

Problems with single case causality criteria:

- plausible timing: may not be known
- de/re-challenge: may not have occurred
- Difficult to exclude other causes or recognise contributory causes
- 'typical' ADR: only a small list of these

Case Series

A case series must contain only comparable reports. i.e. the clinical condition described must be the same

A logical analysis should be applied but this will differ from individual case assessment

***But* individual case assessment is necessary prior to case series assessment**

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Clinical Assessment of Case Series

Consider what each report tells us about

The Patient

The Medical product/s

The ADR/s

Outcome (including dechallenge/rechallenge)

(Seriousness)

What do we know about….

The patient

Demographics, co-morbid conditions, genetics, past medical history, reactions to other medicines

The suspect drug/s

ATC group, dose, dose interval, duration, indication, start/stop dates, formulation, concomitant drugs

The suspected ADR

SOC group, specific condition/symptom, date of onset/recovery, co-reported ADRs

Clinical Assessment of Case Series

We focus on

- Consistency of information
- Pattern recognition
  - *Similarities*
  - *Outliers*

The **Bradford Hill criteria** provide valuable guidance

Sir Austin Bradford Hill

Bradford-Hill A. The environment and disease: association or causation.
Proc R Soc Med 1965;58:295-300

Sir Austin Bradford Hill

Case series causality

Bradford Hill criteria:

- strength of association
- specificity of event
- temporal relationship
- dose response
- consistency of reporting
- biologic plausibility
- experimental evidence
- coherence
- Analogy
  - *Shakir and Layton, Drug Safety 2002.*

Bradford Hill Criteria for Causality in PV

Strength of Association

- Disproportionality measures, relative risks etc (observed>expected)

Temporal relationship

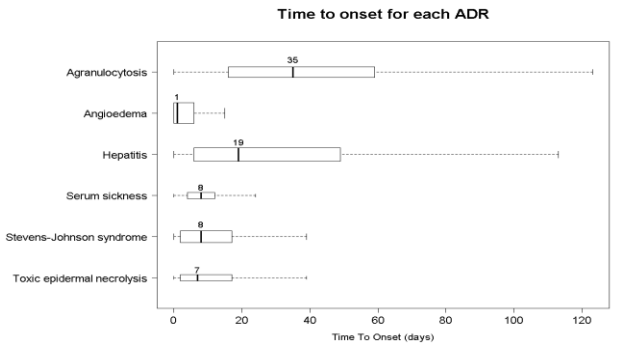
- Commenced after drug started. Fits with pharmacology of drug or host responses (Reasonable time to onset)

Time to onset

Data from VigiBase – reports with single suspect drug, all dates available:

- agranulocytosis 5484 reports
- angioedema 20,930
- hepatitis 8961
- serum sickness 1908
- Stevens Johnson Syndrome 6531
- Toxic epidermal necrolysis 2067
  - *– Khodabakhshi, G. MSc thesis.*

Time to onset



Time to onset

But we don't always know what is a reasonable time to onset!

How do we act in this case?

Look at a case series for consistency

Bradford Hill Criteria for Causality

Consistency

- From a range of reporters or countries, similar observations in reports.

Biologic plausibility

- Fits with what we know about the drug's actions
- Not essential but supportive if present

Biological Plausibility

Biologic plausibility – example 1

An anticholinergic drug may cause urinary retention because the bladder outlet sphincter can't relax. This is most likely to occur if the bladder outlet is already compromised, eg by an enlarged prostate.

If a new drug is reported to cause urinary retention then it would be "biologically plausible" if it has some anticholinergic activity.

Biologic plausibility

Biologic plausibility – example 2

Profound immunosuppression with a tumour necrosis factor (TNF) inhibitor and reactivation of tuberculosis.

But,

often the mechanism is unknown and observation of an ADR leads to more information about a drug's actions eg fluoroquinolones and tendinitis.

Bradford Hill Criteria for Causality

Coherence

- Fits with existing knowledge, eg frusemide cannot increase blood potassium levels.
- Drugs that are not absorbed are unlikely to cause organ damage
- Investigation results fit together eg patient has dark urine and liver function tests show hyperbilirubinaemia.

Bradford Hill Criteria for Causality

Dose-response relationship

If most patients at high end of dose range, or onset on dose increase, or recovery on dose decrease. Also consider if duration-related.

Specificity

ADRs - Many ADRs have multiple causes, eg headache, abdominal pain, renal failure. Generally drugs cause ADRs through specific mechanisms. *In a case series we may start to see a cause through co-reported ADRs eg renal failure and interstitial nephritis.*

Drugs - Are a number of drugs suspect or just one or two?

Investigation results - eg drug-specific antibodies

Bradford Hill Criteria for Causality

Experimental evidence

- eg Prolonged QTc interval

Analogy

- Similar reactions observed with other members of the drug's ATC group, eg
  - combined oral contraceptives and venous thrombosis
  - Angiotensin converting enzyme (ACE) inhibitors and angioedema

Uppsala Monitoring Centre – building a global safety culture

Bringing it all together

- Aronson JK, Ferner RE. Joining the DoTs: new approach to classifying adverse drug reactions. BMJ 2003;327(7425):1222-5.
- Perrio et al. Drug Safety 2007;30(4):333-246
- Ferner R, Aronson JA. EIDOS: a mechanistic classification of adverse drug effects. Drug Safety 2010;33:15-23.
- Edwards IR. Causality assessment in pharmacovigilance: still a challenge. Drug Safety, on-line, 2017.

Uppsala Monitoring Centre – building a global safety culture

Mianserin and agranulocytosis

Mianserin and agranulocytosis in New Zealand

David M. Coulter I. Ralph Edwards

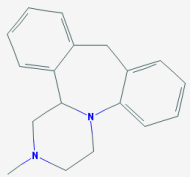
Uppsala Monitoring Centre – building a global safety culture

Mianserin is a **tetracyclic** piperazinoazepine; mirtazapine was developed by the same team of organic chemists and differs via addition of a nitrogen atom in one of the rings.

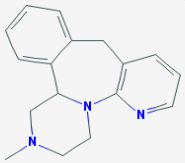
Uppsala Monitoring Centre – building a global safety culture

Chemical Structures: Mianserin and Mirtazapine

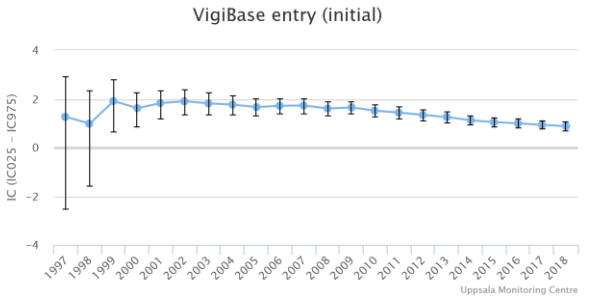
mianserin



mirtazapine



Data Mining. Mirtazapine and neutropenia



Mirtazapine and neutropenia

National databases & Vigibase - Search principles

Ensure find all reports for the **drug/s** of interest - search for drug as a substance.

View ATC group (tetracyclic antidepressants).

Ensure find all reports of the **diagnosis**. View SOC to be sure eg ¨neutropenia¨, ¨neutropenia septic¨, ¨agranulocytosis¨

Be specific in your analysis. Neutropenia, not leukopenia (all white cells).

(For older reports can include granulocytopenia which is neutrophils, basophils and eosinophils)

Mirtazapine and neutropenia
Vigibase reports

Total assessed reports	**21**
Number of countries	**7**
Duplicate	**1**

Mirtazapine and neutropenia
Vigibase Reports

Patient Characteristics

Males/females (20 patients)	5/15
Age (yrs) (20 patients)	
• Range	17-94
• Median	56.5
Indication (6 Patients)	
• Depression	6
Co-morbidities (other illnesses)	
• None relevant	

Mirtazapine and neutropenia
Vigibase reports

Drug Characteristics

Sole suspect medicine	**14**
Daily Dose (mg) (16 patients)	
• 15 mg	2 patients
• 30 mg	9 patients
• 45 mg	3 patients
• 60 mg and 90 mg	2 patients
Time to onset (days) (19 patients)	
• Range	2 to 156
• Mean	47.5
• Median	31.0
• All within six months	

Mirtazapine and neutropenia
VigiBase reports

Drug Characteristics continued

12 reports included co-suspect drugs or concomitant drugs that could have caused the neutropenia.

There was no consistent pattern of co-reported drugs that would suggest an interaction.

No concomitant medicines suggested patients were taking chemotherapy or had blood disorders.

Mirtazapine and neutropenia
VigiBase reports

ADR Characteristics

Additional ADRs

Thrombocytopenia	3
Anaemia, Hb decreased	2

Seriousness

Agranulocytosis (life-threatening)	3

Mirtazapine and neutropenia
VigiBase Reports

Outcomes

- Recovered 13
  - *(Recovered and mirtazapine sole suspect)* *(9)#*
- Not yet recovered 5
- Unknown 2

 # but in one a concomitant medicine was suspect

Basic Problems

- **General uncertainty in medical diagnosis**
- **No diagnostic markers or lab tests demonstrating the role of a drug in a disease**
  - *Except overdose/subtherapeutic drug levels if ADR can be tied to pharmacokinetic parameters*
- **Drug-induced disease (ADR) often cannot be distinguished from natural disease**

Mirtazapine and neutropenia
Vigibase reports

Summary

Outcome

Recovered on mirtazapine dechallenge – no alternative explanation **8**

Not yet recovered, mirtazapine sole suspect **2**

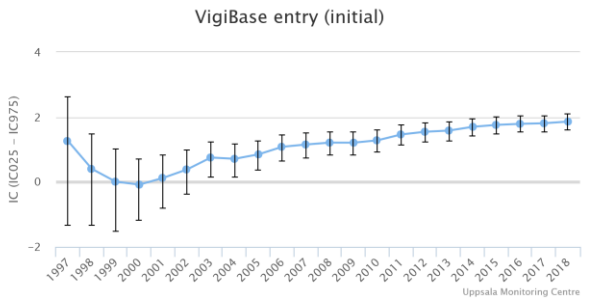
(but reports show concomitants that may have been the cause even though not coded as co-suspect)

Seriousness

Agranulocytosis **3**

(Mirtazapine not sole suspect in agranulocytosis reports but the signal strengthened statistically later and this was clinically confirmed)

Data-mining. Mirtazapine and agranulocytosis



Mirtazapine and neutropenia

CAVEAT

What is missing??

Actual neutrophil counts needed if investigating these reports

Mirtazapine and neutropenia
What would Dr Bradford Hill think?

Summary of evidence and comparison with Bradford Hill criteria

- Statistically disproportionate - strength of association
- Onset within six months, usually shorter. – consistent time to onset and in keeping with expected time to onset of drug-related neutropenia
- Concomitant or suspect medicines were an alternative explanation in more than half of the reports but mirtazapine sole suspect in 7/20 reports - specific
- 7/20 patients with mirtazapine as sole suspect had recovered or improved at the time of reporting – reasonable time to recovery
- Reports from seven countries - consistency
- Neutropenia is a recognised typical adverse drug reaction - biologic plausibility
- Mianserin - Analogy

So,

Did the drug do it?

Does mirtazapine cause neutropenia?

Did the Drug Do it?

The answer is almost never, Yes, definitely

The logic is probabilistic, weigh up all the factors, assess the probability or likelihood.

The Simple Question

Is there any other way of explaining this set of data? Is there any other answer equally, or more likely, than cause and effect?

There are no clear alternative explanations, apart from mirtazapine, for neutropenia in more than one third of the reports in this case series.

Is this a signal?

2010, second quarter of year - Diltiazem/rhabdomyolysis. IC $_{025}$ > 0 in Vigibase.

Number of reports – 55

Did the drug do it?

Some reports of rhabdomyolysis with diltiazem in Vigibase

Country	Concomitant medicines
Australia	Simvastatin, gemfibrozil
Spain	Simvastatin
Netherlands	Simvastatin Metoprolol Paroxetine
New Zealand	Simvastatin Azathioprine Nitro- furantoin
Australia	Simvastatin Ciclosporin Colchicine

Some reports of rhabdomyolysis with diltiazem in Vigibase

Rhabdomyolysis is a severe myopathy with muscle breakdown and therefore myoglobin in the urine which can cause renal failure. It is often fatal.

It is a known dose-related reaction to simvastatin but occurs very rarely at standard simvastatin doses eg 10 and 20 mg daily.

The risk is increased if interacting medicines increase exposure to simvastatin through inhibition of CYP 3A4 enzymes

The reports suggest that simvastatin was the cause of the rhabdomyolysis

Diltiazem is a weak CYP 3A4 inhibitor and is **not** thought to interact to a clinically important extent at standard daily doses of simvastatin

Some reports of rhabdomyolysis with diltiazem in Vigibase

Country	Concomitant medicines	Simvastatin daily dose (mg)
Australia	Simvastatin, gemfibrozil	40
Spain	Simvastatin	80
Netherlands	Simvastatin Metoprolol Paroxetine	60
New Zealand	Simvastatin Azathioprine Nitro-furantoin	40
Australia	Simvastatin Ciclosporin Colchicine	5

Some reports of rhabdomyolysis with diltiazem in Vigibase

The additional information in the last slide shows that all but one patient were taking greater than 20 mg simvastatin daily. At these doses the interaction with diltiazem is clinically important.

One patient was also taking a fibrate, gemfibrozil, which also increases the risk of rhabdomyolysis

One patient was only taking 5 mg simvastatin daily but was taking a strong CYP 3A4 inhibitor, cyclosporin.

The Question

Is there any other way of explaining this set of data? Is there any other answer equally, or more likely, than cause and effect?

- Evidence in the case series suggests that diltiazem does not directly cause rhabdomyolysis.
- It is likely that rhabdomyolysis occurred because diltiazem had a clinically relevant interaction with simvastatin when simvastatin was taken at greater than standard daily doses

Acknowledgment

Thanks to my colleague Dr Ruth Savage at UMC and Otago University for sharing her slides.

References for chemical structures

https://pubchem.ncbi.nlm.nih.gov/compound/mianserin#section=Top

https://pubchem.ncbi.nlm.nih.gov/compound/mirtazapine