SHORT COMMUNICATION

Drug Safety 2002; 25 (6): 433-439
0114-5916/02/0006-0433/$25.00/0

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Signal Generation in the New Zealand Intensive Medicines Monitoring Programme

A Combined Clinical and Statistical Approach

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Abstract

The New Zealand Intensive Medicines Monitoring Programme (IMMP) undertakes prospective observational cohort studies on selected new drugs in the early postmarketing period using prescription-event monitoring (PEM) methodology with the purpose of identifying signals of previously unrecognised ADRs and establishing risk profiles for each drug.

Events are reviewed by a physician and a relationship is established between each event and the drug. The events are then sorted into reactions and incidents. The latter are used to assist signal detection and control for bias. Rates for reports, reactions and incidents are used to assess the adequacy of reporting, signal detection and identification of confounders.

Most signals are identified by clinical evaluation of the reports at a stage when statistical analyses are unlikely to have the power to detect them with confidence. The incident group is used for signal detection and controlling for bias. A low reporting rate indicates that certain types of event are unlikely to be reported.

A systematic review of the original case reports at the site of collection provides the best opportunity for early signal detection. More resources need to be invested in the training and support of clinical evaluators. Categorising events into reactions and incidents gives added value to the data. Rates of reporting should be quoted with the results of cohort studies to facilitate assessment of their power to detect new signals.

There is world-wide emphasis on developing automated search tools with analytical programmes for the detection of new adverse drug reactions (ADRs). These are variously designed for population databases, cohort studies and large databases of adverse reactions. They are essential developments, but the value of systematic, standardised, informed and careful clinical review of the original case reports at the site of collection needs continued emphasis. Most signals should be raised earlier with routine clinical evaluation than by automated methods. Where case reports are small in number, clinical suspicion of a signal may be aroused and investigation instituted before databases have sufficient numbers for adequate power to draw statistical conclusions. On the other hand, automated databases, such as the very large WHO database, maintained at the Uppsala Monitoring Centre (the WHO Collaborating Centre for International Drug Monitoring), and mined using a

Bayesian confidence propagation neural network (BCPNN) as an analytical tool, are an essential insurance against missed signals and an ideal mechanism for validating clinical suspicions of a new ADR. This paper focuses on the methods of signal detection used in the observational cohort studies undertaken by the New Zealand Intensive Medicines Monitoring Programme (IMMP). These are based on the clinical evaluation of each report.

The method of clinical evaluation, collation and analysis of the adverse events reported is described. The use of an hierarchical events dictionary and the value of separating the events into reactions and incidents is illustrated. This allows for between drug and within drug controls, reduces the risk of confounding by reporting bias and lessens the likelihood of missing signals.

The value of using reporting rates in interpreting individual studies and in comparing the results of different studies is described. Certain types of events are less likely to be reported when reporting rates are low, which means that studies with different reporting rates will not be comparable and signals from studies with high reporting rates may not be confirmed by studies with lower reporting rates. An analysis of IMMP data is used to illustrate this.

1. Methodological Approach to Prescription-Event Monitoring

The IMMP undertakes prospective observational cohort studies on selected new drugs in the early postmarketing period using prescription-event monitoring (PEM) methodology with the purpose of identifying signals of previously unrecognised ADRs and establishing risk profiles for each drug.[1,2] Doctors have the option of sending in spontaneous reports and for some drugs, IMMP 'intensified spontaneous reporting' has been undertaken in certain regions of New Zealand; resources are inadequate to conduct PEM throughout the whole country.

All events are assessed by a physician using the same process as for reviewing ADR reports in the spontaneous reporting programme. A 'relationship' is established between the drug and the event according to the guidelines for causality assessment provided by the Uppsala Monitoring Centre.[3] The relationships are coded as 'certain', 'probable', 'possible' or 'unlikely' and the codings are largely dependent on the amount and type of information provided, particularly in relation to the duration to onset of the event from the time of initial drug exposure and the response to dechallenge and rechallenge. The term 'relationship' assessment is used in preference to 'causality' because the basic effect of the clinical review of each report is to establish the strength of the association between a drug and each event. Causality can only be established with confidence after confirmation by other similar observations and/or epidemiological studies. Lack of knowledge of a plausible mechanism of pharmacological action is not considered to be a barrier to the identification of a signal. There is incomplete knowledge of the actions of new drugs and the identification of a new adverse reaction may reveal previously unsuspected pharmacological activity.

The events coded as above are categorised into two groups for further study: (i) those that have been assigned a relationship of certain, probable or possible; and (ii) those that have been given a relationship of unlikely. The former are referred to as 'reactions' and the latter are called 'incidents' because on initial review it appears that their occurrence is incidental to the use of the drug. In the absence of unrecognised reactions, the incident group should represent the background 'noise', which should be determined largely by the condition being treated and other background morbidity, some of which would reflect the age distribution of the cohort. If there are significant differences from the cohort or comparator, then an unsuspected reaction may be signalled from within this group.

For each drug monitored, rates per 1000 patients are calculated for the numbers of: (i) reports; (ii) all events; (iii) reactions; and (iv) incidents, respectively, in total and by gender. If PEM is not conducted nationwide, rates are also calculated by

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spontaneous and PEM regions. PEM has (or is being) conducted nationwide in 14 of the 39 monitoring studies undertaken. The overall reaction and incident rates are useful for comparing sub-groups and for between-drug comparisons, but in contrast to rates for individual events, do not provide a specific measure of risk because some patients have several events associated with the one report. Because comparator drugs should have similar incident rates (i.e. similar background noise), differences in these rates may indicate the presence of an unrecognised reaction, or bias by selective reporting or indication. The incident rates are therefore useful in signalling an unsuspected adverse reaction or in assisting in the evaluation of a signal.

During the clinical review and coding of the events, each event is given a term using the IMMP events dictionary. This dictionary is an hierarchical terminology based on the WHO adverse reactions terminology (WHO-ART). The hierarchy has five levels and events can be sorted at each level in their clinically related groupings, or individually. There are approximately 2600 event terms in the dictionary. The events are classified according to system-organ class and profiles are prepared to provide a visual representation for comparison using the different rates referred to above. Any unexpected differences between comparators are investigated.

A suspicion of a signal is called an alert. The evolution of an alert to a validated signal to a confirmed reaction may be gradual or rapid depending on the numbers and quality of the reports. When numbers are small the very large WHO database is the first and most important point of reference for other reports which may strengthen the alert or signal. Some signals are validated directly by follow-up studies on the cohort.

In order to demonstrate the significance of the reporting rate on the on the ability to detect signals, the rates of reporting of individual events from PEM and intensified spontaneous reporting are compared using rate ratios.

2. Aspects of Signal Identification Illustrated

This section illustrates: (i) the development of signals by clinical evaluation; (ii) the use of incidents in the recognition and evaluation of signals; and (iii) the effect of the reporting rate on the likelihood of detecting signals.

2.1 Clinical Development of Signals

2.1.1 Interaction of Celecoxib and Amitriptyline

The following case reports were regarded as alerts of a possible signal. The reports suggesting a signal of interaction between celecoxib and amitriptyline were received spontaneously before any questionnaires were sent out. In the first case report, a 60-year-old woman, who was taking long-term amitriptyline 10mg regularly at night, began taking celecoxib 100mg twice daily. She became nauseated every time she took celecoxib with the amitriptyline, but not with the morning dose. Celecoxib inhibits the CYP450 2D6 isoenzyme and amitriptyline is metabolised in part by the same enzyme. Although this was a minor event, the strong relationship and the plausible mechanism were of interest. In the second report, a 45-year-old woman had been taking long-term amitriptyline (dose not stated) and 3 days after commencing celecoxib 200 mg/day she developed 'rapid runs of supraventricular tachycardia'. These ceased within 24 hours of stopping celecoxib.

The WHO database was searched for reactions reported with the concurrent use of celecoxib and amitriptyline. Four case reports were found, all involving women: (i) age 70; tachycardia occurred one day after the addition of amitriptyline to treatment with celecoxib of unknown duration; (ii) age 48; palpitations began one month after the addition of celecoxib to long-term amitriptyline; (iii) age 33; 1 day after the addition of celecoxib to long-term amitriptyline the patient developed tachycardia, chest pain and dyspnoea; and (iv) age 61; 1 day after the addition of celecoxib to long-term amitriptyline, the patient developed palpitation, tremor and diarrhoea. It was considered that the

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supporting evidence of the WHO data raised the status of the alert to a signal.

2.1.2 Pain Activation with Sumatriptan

Six case reports were received with PEM of the development of severe pain a few minutes after the use of subcutaneous sumatriptan 6mg at sites of recent trauma (up to 1 month previously). The injuries included sunburn, superficial scratches, recent surgery, haematoma and fracture. The database was then examined for other events associated with severe pain and a number of reports were identified of severe pain developing at sites of inflammation. The conditions included rheumatoid arthritis, 'colitis', toothache, ear pain and sacro-iliac pain. The events were always rapid in onset and some were severe. This syndrome was considered to be a strong signal of a new adverse reaction.

2.1.3 Signals with Omeprazole

Table I lists signals identified in a similar manner to those outlined in sections 2.1.1 and 2.1.2 during the monitoring of omeprazole. These events were considered to be signals if there had been no more than one prior publication reporting a similar event and if there had been sufficient concern to draw them to the notice of the New Zealand Medicines Adverse Reactions Committee (MARC), which has an advisory function to the Ministry of Health. The IMMP signals were documented in MARC meeting documents.

Table I. Signals identified for omeprazole in the Intensive Medicines Monitoring Programme

Ageusia/dysgeusia
Amnesia
Angioedema/urticaria
Bone marrow depression
Carcinoid tumour
Confusion
Diarrhoea
Dry mouth
Extrapyramidal events
Gastric polyps
Gum pain/hyperplasia
Gynaecomastia/galactorrhoea
Hallucinations
Headache
Hepatic events
Hyponatraemia
Impotence
Interstitial nephritis
Myalgia
Paraesthesia
Polymyositis
Polyuria/polydipsia
Rash/pruritus
Vitamin B12 deficiency
Vomiting/nausea

2.2 Use of Incidents in Signal Recognition and Evaluation

2.2.1 Signal Recognition

Simvastatin, gemfibrozil and bezafibrate were monitored as part of IMMP concurrently. Examination of the incident profile for bezafibrate showed an unexpected peak in the cardiovascular system/organ class. This was shown to be due to a statistically significant increase in angina when compared with the other two drugs. A signal validation study from the cohorts of these three drugs confirmed an excess of angina in patients receiving bezafibrate, but showed that this was caused by confounding by indication. Bezafibrate had been prescribed preferentially for patients with diabetes mellitus and more patients in the bezafibrate group had hypertension.[4] Both conditions are risk factors for ischaemic heart disease.

2.2.2 Incidents as Within-Drug Control

The rates of adverse reactions were higher in women than men receiving moclobemide (relative risk [RR] 1.7; 95% confidence interval [CI] 1.4 to 2.0) and fluoxetine (RR 1.7; 95% CI 1.3 to 2.2). There was no significant gender difference seen in the incident rates. It would appear therefore that the gender difference seen for the reactions is a true risk factor and not due to reporting bias.

2.2.3 Incidents as Between-Drug Controls

The results of monitoring omeprazole showed a very low rate of reactions. However the incident rate was higher than for other drugs monitored con-

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currently, suggesting again an absence of confounding because of a low reporting rate and a consequent strengthening of the finding (table II). Table III illustrates further the use of incidents as between-drug controls. A signal had been raised elsewhere of inflammatory arthritis with omeprazole. Comparison of concurrently monitored drugs showed that the rate of arthralgia/arthritis/synovitis for omeprazole was in the lower range. The incident rate however was higher and thus reporting bias was unlikely. This suggested that these reports represented background morbidity or an incidence that was no greater than the other five drugs used as comparators.

2.3 The Potential Effect of Reporting Rates on Signal Identification

In each IMMP study where there has been intensified spontaneous reporting and PEM reporting, the rate has been very much higher with PEM, usually of the order of 10- to 12-fold greater. The rates for specific events were compared and some are shown in table IV. These data come from the cohorts of seven different drugs. There were 16 790 patients in the PEM group and 39 937 in the group from which events were reported spontaneously. Angioedema/urticaria, extrapyramidal effects and blood dyscrasias were as likely to be reported spontaneously as with PEM. Conversely, dry mouth, dyspepsia, death, myocardial infarction and asthma were by comparison, very unlikely to be reported spontaneously. Other events ranged between these two extremes. It needs to be emphasised that this refers to IMMP 'intensified' spontaneous reporting which has a higher rate of reporting than the standard spontaneous reporting programme in New Zealand.

Table II. Incidents as between-drug controls: comparison of monitoring rates (%)

	Reactions	Incidents	Total
Omeprazole	2.7	13.6	16.3
Moclobemide	9.8	7.6	17.4
Fluoxetine	12.6	7.0	19.5
Bezafibrate	12.4	9.5	21.8
Gemfibrozil	10.8	8.4	19.3
Simvastatin	7.7	9.1	16.8

Table III. Incidents as between-drug controls: arthralgia/arthritis/synovitis

	Reactions/1000 patients	Incidents/1000 patients
Omeprazole	0.7	135.7
Moclobemide	0.6	75.7
Fluoxetine	0.9	69.8
Bezafibrate	1.1	94.7
Gemfibrozil	1.0	84.3
Simvastatin	1.5	90.8

3. Discussion

Almost all of the signals identified in the IMMP have been recognised by routine clinical evaluation of reports received as demonstrated in the examples given of the interaction between celecoxib and amitriptyline, and of pain activation with sumatriptan. Simple statistical analyses as outlined are performed on the data routinely, but only one additional signal has been found through this process in 25 years of operation. Experience in the IMMP suggests that careful standardised clinical assessment of the reports at the time and site of collection will produce signals earlier than relying on statistical analyses at a later stage when a larger aggregation of reports may contain sufficient numbers to achieve adequate statistical power for identification. The very large international WHO database is an ideal resource for validation studies and for identifying signals that have been missed. More resources need to be invested in the training and support of competent clinical evaluators and their training needs to develop the methods and skills needed for signal recognition.

Statistical methods of signal recognition rely on the application of appropriate adverse event/reaction terminology in the assessment of the original reports and these need to be applied consistently. Signals may be lost when there is no appropriate reaction term or where the same basic event may

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Table IV. Examples of rate ratios of reporting of specific events: prescription-event monitoring versus spontaneous reporting

Specific events	Rate ratio (95% confidence interval)
Rate ratio <2	
Angioedema/urticaria	0.6 (0.25-1.52)
Extrapyramidal events	0.6 (0.21-1.91)
Blood dyscrasias	1.6 (0.44-3.94)
Rate ratio 2-5	
Rash	2.5 (1.3-4.8)
Renal failure	2.6 (1.2-5.7)
Cardiac dysrhythmia	3.1 (1.1-8.2)
Liver abnormality	3.5 (1.7-7.1)
Impotence	3.8 (1.7-8.4)
Arthralgia/arthritis	4.8 (2.1-10.6)
Rate ratio 5-10	
Headache	6.3 (4.0-9.9)
Anxiety/agitation	9.8 (5.0-18.9)
Rate ratio >10	
Dry mouth	10.1 (3.4-30.1)
Dyspepsia	11.4 (7.0-18.4)
Heart failure	40.6 (12.7-130.0)
Death	57.8 (34.5-97.0)
Angina/myocardial infarction	126.9 (31.3-514.0)
Asthma/chronic obstructive pulmonary disease	Infinity

have various expressions as in the example given of 'pain activation' with sumatriptan. Clinical review of each of these case reports identified a signal for which there was no adequate adverse reaction term. It is likely that the signal would have been missed in the absence of clinical evaluation identifying a specific association between prior trauma or inflammation and activation of pain following injection. These reports may well have been masked by being buried under many other reports of pain, or a variety of nonspecific terms, with the likelihood that statistical analysis would have missed the signal. The Uppsala Monitoring Centre administering WHO-ART, introduced two new terms to identify the signals: 'pain trauma activated' and 'pain inflammation activated'. The keys to rapid signal detection are therefore: (i) careful clinical analysis; and (ii) a terminology that has terms as specific as possible and can adapt quickly.

The separation of events into reactions and incidents can be seen as a type of triage and results in more homogeneous groups: one group that appears to have a relationship with the use of the drug and another that does not appear to be related to drug use. If these two groups are analysed together there is potential for masking of signals by dilution of the reactions with the background noise. The same applies to the characterisation of reactions e.g. typical duration to onset or gender as a risk factor. The categorisation of reactions and incidents gives added value to the data.

The demonstration that the rate of reporting affects the event profiles of a drug indicates that it is important to quote the rate in order to allow good interpretation of the data. Studies with low reporting rates are likely to miss certain types of events. It follows therefore that studies on specific drugs are not comparable unless the reporting rates are similar. Differences in study results may be explained by differences in reporting rates. This is important in signal identification and strengthening or validation. It is a well established principle that one observation needs to be confirmed by others and it should be helpful in interpretation, if differences can be understood in terms of rates of reporting. The incident reporting rate is of value in assessing the completeness of reporting and in demonstrating the presence or likely absence of reporting bias or other confounders. It should be similar between comparator drugs in the absence of bias. A careful analysis of the incident group provides the opportunity for identifying signals missed during clinical evaluation.

4. Conclusions

There is a variety of methods of signal identification which can be divided into two main groups: clinical and statistical evaluation. Recently much emphasis has been given to the development of automated statistical methods. Both types of method are essential and complementary. Because the ear-

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liest opportunity for signal identification is at the time and point of collection of reported events, more resources need to be given to training in standardised procedures for clinical review of the events and the evaluation of signals identified as a result. This needs to be accompanied by the provision of adequate numbers of trained staff in monitoring centres.

Acknowledgements

The Intensive Medicines Monitoring Programme is funded by the New Zealand Ministry of Health with additional grants from several different pharmaceutical companies.

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