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Thoughts on Signal Detection in Pharmacovigilance

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"*We shouldn't overload the disproportionality methods; putting them in perspective will provide the maximum benefit*."

A drug safety signal is not necessarily entirely new information about a potential drug safety hazard, it can be additional information (either quantitative or qualitative) about a previously known drug/event association: for example, new information about a risk factor for an adverse drug reaction (ADR), a sub-population being at an increased risk of developing an ADR or information about a dose-effect relationship for an ADR.

1. Sources of Signals

An important source of signals in drug safety has been, and will continue to be, the observations of clinicians who make a diagnosis of a possible ADR. Published case reports and case series are a very important source of signals, the letter from McBride to *The Lancet*[1] in 1961 raising concern about the teratogenicity of thalidomide is an excellent example. However, sometimes the time from identification to publication of case reports can be excessively long. Journal editors need to consider ways to expedite publishing case reports of suspected ADRs. Increasing use of web publishing creates opportunities to facilitate rapid dissemination of these reports. Pharmacovigilance departments within pharmaceutical companies and regulatory authorities must have robust systems to capture published case reports by monitoring the published literature.

2. Spontaneous Reporting

An important aim of monitoring the safety of a medicine is to identify reports or clusters of reports that raise suspicion of ADRs. Such reports need assessment to decide the likelihood of them being true ADRs.

Recently, automated methods have been used to mine databases of spontaneous reports to detect drug safety signals. However, signal detection is not exclusive to spontaneous reporting systems. Observational databases and data from clinical trials can also provide useful sources for detecting safety signals.

In searching for signals, clinical and pharmacological knowledge about the disease and the drug are essential. As elsewhere in medical sciences, it is more likely to find signals if one knows what to look for. Signal detection and evaluation must be based on clinical and pharmacological knowledge. Shifting the emphasis of signal detection to statistical methods with little biological consideration is inappropriate. In signal detection in pharmacovigilance, as with elsewhere in medicine, the role of statistics is to work with and support biological methods not to replace them.

3. Established and New Drugs

It is true that in the drug-event matrices of national postmarketing pharmacovigilance databases many cells are populated with low counts (three or fewer reports) and the assessment of such reports for established products is a low-yielding exercise. Therefore, statistical methods of disproportionality (especially those that are effective in handling small

numbers) may be a useful way to detect signals for established drugs (drugs that have been in use for a long time). However, the strengths and weaknesses of this approach to generate signals for these drugs need to be examined.

However, different approaches are required for signal detection for new drugs. The main method for signal detection for this group of drugs must be based on clinical and pharmacological knowledge. From a patient safety perspective, the importance of signal detection for new drugs necessitates employing adequate numbers of appropriately trained staff to work on signal detection. Staff working on signal detection for new drugs must be familiar with the pharmacological and clinical aspects of the drug including the relevant findings in animal studies and clinical pharmacology studies as well as pre- and postmarketing clinical studies. Knowledge of the safety profiles of other products in the same therapeutic class and clinical knowledge about the underlying and any related diseases are necessary. All this knowledge ought to lead to focusing the signal detection on areas with higher likelihood of detecting signals. Although the clinically and pharmacologically guided approach to look for likely signals is necessary, it is important to remember that it is always possible for entirely unexpected ADRs to occur.

4. Signal Detection in Prescription-Event Monitoring

Prescription-event monitoring (PEM), which is run by the Drug Safety Research Unit (DSRU), is an intensive monitoring system for the safety of new medicines prescribed in general practice.[2] PEM collects data on cohorts of 10 000–12 000 users of new medicines. Signal detection is one of the objectives of PEM. At the DSRU, the events are reviewed and follow-up information is sought for medically important adverse events (AEs) reported during premarketing development, those reported during postmarketing in other countries, events considered to be possibly associated with the drug, events which cause concern and events occurring during or after pregnancy and deaths with unclear or suspicious cause of death. In addition, follow-up information is sought for medical conditions that have been known to be associated with the use of medicines, e.g. aplastic anaemia.[2]

In addition, statistical and comparative methods are used in PEM to detect drug safety signals. Generally, these methods apply to within-drug analyses (comparing incidence densities of reported events during different periods after starting the drug) or comparisons between drugs in the PEM database.

5. The Relationship between the Incidence of Events with the Drug and the Underlying Illness

An important determinant for the likelihood for detecting ADRs is the relative frequency of the ADR in users of the drug compared with patients with the underlying disease who do not use the drug.

In 1977, Jick[3] proposed strategies to investigate drug safety signals that take into account the frequency of the event in those who received the product and its frequency in the underlying population of non-users of the drug. Briefly, when "a drug commonly induces an otherwise rare illness"; the illness is likely to be detected during the premarketing phase. "A drug which rarely induces an otherwise rare illness"; is what most pharmacovigilance systems aim to address. A "drug commonly inducing an otherwise common illness"; requires a clinical trial, or rigorous and well designed observational studies. Lastly, it is extremely difficult to detect an event when "A drug rarely induces an otherwise common illness".

6. Reactions versus Events

In general, when reporting an ADR, there is a suspicion (even if weak) by the reporter for a possible causal association with the suspected drug. However, those who send reports to spontaneous reporting systems do not always follow this rule; therefore, databases of spontaneous reports include reports of both reactions and events. No suspicion for a causal association is required for reporting AEs. Research is needed to investigate the impact of lumping AEs with ADRs in signal detection by

methods which use statistical disproportionality in spontaneous reporting systems.

7. Signs and Symptoms versus Diagnosis

Postmarketing reports received by pharmacovigilance systems can include signs and/or symptoms with no diagnosis suggested by the reporter as well as reports that include a diagnosis. The diagnosis can be provisional or final. The impact of this heterogeneity on automated signal detection is unknown; research is required to assess it.

8. Follow-up

Since frequently the initial information is incomplete in many ADR/AE reports, follow-up information for selected events is necessary, particularly for signal evaluation. For some events, case definition is required to guide follow-up and enhance signal detection and evaluation. Strategies for follow-up for selected events should be planned at the outset but modified in the light of any relevant, new information.

9. Automated Signal Detection

Several statistical techniques (which collectively have been described as disproportionality methods), such as proportional reporting rates or systems using Bayesian neural networks, have been proposed for automated signal detection in pharmacovigilance. For practical purposes, there are only minimal differences between these systems, e.g. some are better in handling small numbers of reports. Essentially, all these techniques compare the safety profile of a product with the rest of the database to identify events that have been reported proportionately higher with the drug under study compared with all other drugs in the database put together. Events that have been reported proportionately higher for the drug compared with the rest of the database are considered as signals which merit further evaluation. The principal contribution of the method is that it introduces to the spontaneous reporting system a comparative approach (although somewhat limited). Quantitative comparisons between drugs in the spontaneous reporting system are not been possible because of the lack of denominators. However, the benefit and validity of the disproportionality approach are yet to be defined and validated.

The vigilance and intensity of monitoring required for new drugs and drugs about which there are safety concerns, render methods of automated signal detection to be of limited benefit for detecting new safety signals. Pharmacovigilance staff who monitor new drugs are expected to use their medical and pharmacological knowledge to detect drug safety signals earlier than automated signal detection methods can. Similarly, for normally rare conditions that are known to occur with the use of medicines, e.g. aplastic anaemia,[2] automated signal detection is not necessary because such events ought to initiate follow-up and further evaluation without the need for highlighting by any signal detection method.

However, for new drugs, disproportionality methods can be useful to validate signals detected by clinical/biological means or signals detected from other data sources, such as animal studies, clinical trials or observational studies.

In my opinion, the principal benefit of automated signal detection as a first-line method for signal detection is for established products. Automated signal detection can address the problems of small numbers of reports for those products and provide useful support for the limited human resources available to generate signals for these products by other ways.

10. The Threshold

There are no agreed absolute or relative numbers of reports for an event to trigger a signal. Many factors influence whether an event is regarded as a signal, such as the frequency of the event in the users of the drug, the total number of users (the denominator), the frequency of the event in the underlying population without exposure to the drug, the frequency of the event with concurrent drugs and the seriousness of the event. It must be emphasised that the final decision for accepting a causal association of a signal ought to be clinically based. Even with the limitations of medical judgement, in my view, if

applied well in signal detection, it is superior to pure statistical methods. However, the two approaches, the medical/biological and the statistical are not in conflict, they complement each other.

With regard to setting thresholds for disproportionality in automated signal detection, the various methods have proposed statistical thresholds. This has practical advantages as a generic method for signal detection, e.g. for established products. However, the thresholds should not be fixed, they should be altered as necessary, e.g. lowered for life-threatening events.

11. Conclusion

Spontaneous reporting continues to be a very important source for signal detection in pharmacovigilance. In some cases, it is the only source available for detecting rare ADRs.[4] Those responsible for operating such systems have a public health responsibility to provide adequate technical and human resources for running these systems effectively to achieve their full objectives for protecting public health. Automated signal detection must not be seen as an inexpensive replacement for more effective methods of signal detection that require more human resources. From a public health perspective, the best use of automated signal detection is as a complementary method to the other ways of signal detection. Automated signal detection can be applied to observational studies, drug utilisation studies and clinical trials.

Automated signal detection is evolving, it is moving from the phase of research and development to practical application. More will be learnt about the effectiveness of this approach, its strengths and weaknesses. Methodological research is required to examine its effectiveness and define its role in the pharmacovigilance process.

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