CONFERENCE PAPER

Drug Safety 2007; 30 (7): 607-609
0114-5916/07/0007-0607/$44.95/0

Signal Detection
Historical Background

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Abstract

A primary aim in pharmacovigilance is the timely detection of either new adverse drug reactions (ADRs) or a relevant change of the frequency of ADRs that are already known to be associated with the drugs involved, i.e. signal detection. Adequate signal detection solely based on the human intellect (case-by-case analysis or qualitative signal detection) has proven its value. However, it is becoming increasingly time consuming given the growing volume of data, as well as less effective, especially in more complex associations, such as drug-drug interactions, syndromes and when various covariates are involved. In quantitative signal detection, measures that express the extent in which combinations of drug(s) and clinical event(s) are disproportionately present in the database of reported suspected ADRs are used to reveal associations of interest. Although the rationale and the methodology of the various quantitative approaches differ, they all share the characteristic in that they express to what extent the number of observed cases differs from the number of expected cases.

Recent years have shown that the use of quantitative measures in addition to qualitative analysis is a step forward in signal detection in pharmacovigilance.

This paper uses historical, classic examples and studies to illustrate the principles, pros and cons of especially quantitative methods in signal detection and adds a flavour of future perspective.

"*The work we are doing is somehow related and builds on the ideas and the work of our predecessors.*"

A primary aim in pharmacovigilance is the timely detection of either new adverse drug reactions (ADRs) or a relevant change of the frequency of ADRs that are already known to be associated with a certain drug, i.e. signal detection.

The objective of signal detection can be phrased in many ways, but two elements have always been important:

- to detect, as soon as possible, any indication of a potential problem with a drug, either a new or an old drug; and
- signals are intended to arouse suspicions and should be followed up with deeper investigation such as formal pharmacoepidemiological studies.

Before powerful computer technology was available, signal detection solely relied upon case-by-case study implying that each individual case report of a suspected ADR submitted to a spontaneous reporting system is reviewed by an experienced assessor. He or she (i) assesses the likelihood that the clinical picture has been caused by the drug, and

(ii) tries to see whether the case report is somehow unusual or strange.

Spontaneous reporting systems collect all possible kinds of reports, and this variance brought the Uppsala Monitoring Centre (UMC) to produce quality criteria for signals.[1] This UMC paper together with the classic Venning publications[2-7] show that collections of individual case reports, including those published in the biomedical literature, are very important for signal detection.

Qualitative signal detection solely based on the human intellect by means of case-by-case analysis has proven its value; however, it is becoming increasingly time consuming given the growing volume of data, and becoming less effective, especially in complex associations, such as drug-drug interactions, syndromes and when numerous covariates are involved. During the past 10–15 years, the availability of powerful IT systems has boosted the development of quantitative signal detection.

Quantitative assessment is all about disproportionality, it enquires: "Is what we observe different from what we expect?"

Historically, the papers of reference are those by Finney.[8] He proposed the development of a method to systematically search through records of suspected ADRs looking for disproportionately frequent combinations of drug(s) and clinical event(s) to reveal associations of interest. He also stressed that such methods are used to arouse suspicions and further investigation is required. The famous letter in *The Lancet*[9] about thalidomide-induced phocomelia is in fact an example of disproportionality. The information provided by McBride is sufficient to construct a two-by-two table and calculate some measures of disproportionality (e.g. an odds ratio or a risk ratio).[8]

When computer technology was not easily available, there was one man who already organised reports of suspected ADRs in a systematic way. Ed Napke designed a cabinet and called it the 'pigeon hole'. Drugs would be distributed in one dimension of the cabinet and ADRs in another. Each drug-event combination had a separate hole in the cabinet. A label was attached to each report, for example, if it was serious or unexpected, producing a kind of visual disproportionality.[10]

The concepts laid out by Finney and Napke were very important when creating computer databases for signal detection in the nineties because computers became readily available. Nowadays, both qualitative and quantitative methods are important for adequate signal detection. However, because of efficiency, we are now more inclined to start with quantitative assessment and then move to qualitative evaluation.

A great deal of work has been carried out on what measure of disproportionality to use. Van Puijenbroek et al.[11] studied whether or not the performance of different measures of disproportionality is different in the presence of three or more reports. Although the rationale and the methodology of the various quantitative approaches vary, the differences in performance were not significant.

Improvements in quantitative signal detection are most likely to originate from taking into consideration the:

- Selection of appropriate control groups and restriction to subsets of people/reports
- Inclusion of aspects of information quality
- Categorising exposure according to (dis)similarities in Structure-Activity Relation (SAR) instead of on the level of active substance, an example given by De Bruin et al.[12]
- Integration of various data sources, such as including patient (direct consumer) reports which has been shown to speed up signal detection[13]
- Better use of 'free text' technology
- Balanced focus between quantitative and qualitative aspects, an example of quantitative/qualitative integration given by Russmann et al.[14]
- Linking expertise in pharmacovigilance and pharmacoepidemiology.

Recent years have shown that the use of quantitative measures in addition to qualitative analysis is a step forward in signal detection in pharmacovigilance. The increasing numbers of signals generated need more resources to be properly evaluated, as well as new and improved methods and systems.

Acknowledgements

No sources of funding were used to assist in the preparation of this paper. The author has no conflicts of interest that are directly relevant to the content of this paper.

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