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Use of Triage Strategies in the WHO Signal-Detection Process

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Abstract

An important role for the WHO Programme for International Drug Monitoring is to identify signals of international drug safety problems as early as possible. Since 1998, Bayesian Confidence Propagation Neural Network (BCPNN) data mining has been in routine use for screening of the WHO adverse reaction database, Vigibase. The identification of drug/adverse drug reaction combinations that have disproportionately high reporting relative to the background of all reports constitutes the first, quantitative step in the Uppsala Monitoring Centre (UMC) signal-detection process.

In order to improve the signal-to-noise ratio and to focus on possible signals that are less likely to be detected by individual national pharmacovigilance centres, an expert group considered a number of possible subsidiary selection algorithms to be added as a second filtering step before potential signals were sent to the UMC expert panel for clinical review. As a result of these deliberations, three selection algorithms were implemented for routine use in 2001: 'serious reaction and new drug', 'rapid reporting increase' and 'special interest terms'.

The effect of applying these algorithms has been critically evaluated on the basis of the ratio of associations selected to signals found and some modifications decided.

Bearing in mind that any filtering strategy is likely to exclude some potential true signals from consideration, we think that triage strategies based on a combination of pragmatic thinking and experience are effective, provided that the results are reviewed at regular intervals and the algorithms adjusted on the basis of performance.

"*The vision of the WHO programme is to 'ensure that effective, timely, international effort will never miss a signal*'".

The role of the Uppsala Monitoring Centre (UMC) and the WHO Programme for International Drug Monitoring is to add to existing knowledge and to complement the work done by national centres, while avoiding duplication of efforts.

The WHO adverse reaction database, 'Vigibase', has a range of advantages. The group of countries participating in the programme extends beyond the International Conference for Harmonisation regions. Each country contributes with their own experience and knowledge, which has accumulated >3.5 million case reports since the inception of the programme. Other advantages are that, in theory, the

database covers all populations, the data are collected continuously and the cost of the system is low.

1. The Signal Detection Process

For >20 years, a group of clinical experts from different parts of the world have actively looked for 'needles in the haystack'. Given the volume of data, it is widely accepted that filtering techniques are necessary.

Since 1998, the signal-detection process in operation at the UMC is based on quarterly Bayesian Confidence Propagation Neural Network (BCPNN) scans. Initially, a list of all drug/adverse drug reaction (ADR) combinations reported in the quarter is produced. Then the associations, a sub-selection of combinations that are statistically disproportionate, are sent for expert evaluation to the 30–35 people review panel. Based on their assessments, pertinent associations are circulated to all national centres in the Signal document.

As an example, in one quarter, 75 000 drug/ADR combinations were added to the database, 20 000 presented associations reported more frequently then expected, this means they passed the BCPNN threshold. Reviewing 20 000 associations manually in one quarter is still too much.

2. Development of Triage Strategies

Additional filtering and improved priority setting were chosen as strategic options to develop triage algorithms on top of the initial BCPNN filtering.

Triage is a process in which things are ranked in terms of importance or priority.

The factors considered to be relevant for signal priority were: (i) ADR unexpectedness; (ii) ADR seriousness; (iii) disproportionality; (iv) rapidly increasing disproportionality (the change of the information component [IC] value over time was considered more relevant than a high value of IC in isolation); (v) newer drugs; (vi) reports from multiple countries ('international signals' are of particular importance to the WHO programme); (vii) special interest reactions (a limited list of events likely to be associated with drugs); (viii) positive rechallenge.

In 2001, a first set of triage algorithms was applied to routine signal detection. These were based on:

- Serious ADRs and new drugs;
- Rapid reporting increases;
- Special interest terms.

Given that the triage algorithms are based on a pragmatic approach and arbitrary cut-off points, recent investigation at the UMC has evaluated the efficiency of the method and the coverage of the different system organ classes.

Using data from 2001–2004, drug/ADR combinations highlighted by the first filtering in the triage were divided as to whether they were referred to in the literature or not. At a later stage, the proportion of candidate signals that were published or circulated in the Signal document was assessed. Reviewers and national centres were also approached using a questionnaire survey.

As a result of the evaluation, it was discovered that an increased number of associations detected by the 'critical terms' algorithm, actually decreased efficiency. The algorithm will be modified to decrease the number of associations signalled.

It was also found that the 'serious ADR and new drug' and 'rapid reporting increase' filters were restrictive and could be expanded by widening their criteria.

Finally, the main finding was that there was some under-representation of several system organ classes in the output. Therefore, three new filters will be developed, one for fetal and neo-natal disorders, a second for neoplastic disorders and a special filter targeting drugs on the WHO Essential Drugs list.

On the whole, both reviewers and national centres were satisfied with the new triage system. Reviewers felt they could concentrate on signal candidates that were more likely to be true signals. The national centres rated the relevance, importance and usefulness of the circulated signals as 'good'.[1]

3. Data Quality

Often one talks about the wonderful systems in place and all the potential uses of the reported information. Ideally, data are expected to be relevant,

precise and complete. In the real world, we deal with data that are transferred and every data exchange potentially leads to loss of quality.

Previously, the UMC system had a tight rigorous quality check of the incoming data. Many reports were rejected at the entry point and much staff-time was spent correcting reports. Nowadays, all reports are entered promptly as they arrive, it is important that they are in the database early on. Afterwards, they can be labelled according to the level of data quality (relevance, completeness, consistency, precision, accuracy). These parameters can then be used for signal detection and triage and also for quality control. Additionally, the new philosophy is useful for feedback to the national centres. The first documentation grading system has been in place since the publication of a related article,[2] more advanced grading is yet to be implemented.

There are differing views as to whether under-reporting or over-reporting is a greater problem. In regard to mechanisms that generate (selective) over-reporting, one can always take action, although it is more difficult to contend with under-reporting.

4. Conclusions

Filtering techniques are crucial, particularly for signal detection in large databases.

At the UMC, the automated part of signal detection is deeply intertwined with the human element; the aim is to take into account both the clinical information from case reports as well as the baseline quality of the data.

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