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Application of Quantitative Signal Detection in the Dutch Spontaneous Reporting System for Adverse Drug Reactions

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Abstract

The primary aim of spontaneous reporting systems (SRSs) is the timely detection of unknown adverse drug reactions (ADRs), or signal detection. Generally this is carried out by a systematic manual review of every report sent to an SRS. Statistical analysis of the data sets of an SRS, or quantitative signal detection, can provide additional information concerning a possible relationship between a drug and an ADR. We describe the role of quantitative signal detection and the way it is applied at the Netherlands Pharmacovigilance Centre Lareb. Results of the statistical analysis are implemented in the traditional case-by-case analysis. In addition, for data-mining purposes, a list of associations of ADRs and suspected drugs that are disproportionally present in the database is periodically generated. Finally, quantitative signal generation can be used to study more complex relationships, such as drug-drug interactions and syndromes. The results of quantitative signal detection should be considered as an additional source of information, complementary to the traditional analysis. Techniques for the detection of drug interactions and syndromes offer a new challenge for pharmacovigilance in the near future.

Despite extensive research and large premarketing trials, only limited information concerning the adverse drug reactions (ADRs) of a drug is available at the time of marketing. For this reason, there is a need for continuous systematic surveillance for unexpected ADRs. In recent decades, spontaneous reporting systems (SRSs), used to monitor the safety of drugs after marketing, have earned a reputation for offering a fast and reasonably (cost)-efficient way of detecting ADRs.[1] Physicians and pharmacists report suspected associations between ADRs and drugs to an SRS on a voluntary basis. The process of signal detection, i.e. the search for unexpected associations, is usually carried out by means of a systematic manual review of all reports sent to an SRS. In this process, more complex associations between patient characteristics, the reported ADR(s) and suspected drug(s) are difficult to recognise.

Because of the 'spontaneous' character of the reporting, the method has some limitations. The most noticeable problem is (selective) underreporting, which may be caused by various factors. Moreover, not all reported suspected ADRs actually do represent true ADRs.

Methods applied in analytical epidemiology, such as the case-control design, which are primarily used for the evaluation of signals, may also serve as techniques for signal detection. Statistical quantitative approaches can be efficient tools to analyse the data set of an SRS and help minimise the risk that possible signals are missed. Quantitative analysis, being the statistical analysis of the data sets of an SRS, can provide additional information concerning a possible relationship between a suspected ADR and a drug. Several approaches have been introduced, for instance signalling changes in trend or the 'reaction proportion signalling', introduced by Finney, which involves the comparison of records of a single drug and suspected ADR with those of a larger set of drugs and reactions.[2-4] Over the years, modifications of the latter approach have been developed, such as the proportional ADR reporting ratio[5-7] and the reporting odds ratio.[8-10] More recently, more complex methods were introduced. The WHO Centre for International Drug Monitoring (Uppsala Monitoring Centre [UMC]) uses a so-called Bayesian Confidence Propagation Neural Network (BCPNN),[11] and the US FDA uses a Multi-Item Gamma Poisson Shrinker programme.[12] Also, these two approaches are being used to highlight associations that stand out as being different from the generality of the database.

Despite the increasing popularity of these new approaches, their integration with the traditional case-by-case analysis is still not routinely implemented for every centre. At the Netherlands Pharmacovigilance Centre Lareb, quantitative signal detection has been used in various ways.[13] We describe the place of quantitative signal detection and the way it is applied in this centre and discuss limitations and advantages of this approach.

1. Quantitative Signal Detection at the Netherlands Pharmacovigilance Centre

Each report received by the Netherlands Pharmacovigilance Centre, maintaining the national SRS on behalf of the Dutch Medicines Evaluation Board, is subjected to review by qualified assessors. Data concerning the suspected ADR(s) and drug(s) are coded using the WHO adverse drug reaction terminology (WHOART)[14] and the anatomical therapeutic chemical (ATC) coding system, respectively, and subsequently filed in a database. At 1 November 2002, the database contained about 31 786 reports. If the suspected ADR is mentioned in the Dutch reference textbooks 'Farmacotherapeutisch Kompas'[15] or the 'Informatorium Medicamentorum'[16] the ADR is considered labelled, if it is not mentioned in these reference books it is considered unlabelled. These textbooks generally cover the Summary of Product Characteristics (SPC), but in contrast to the original SPC, they are more easily accessible for the majority of physicians and pharmacists. On a weekly basis, about 60 new reports are discussed on a case-by-case basis in an assessment meeting. In this meeting potential relevant associations (signals) are selected for possible dissemination to the Medicines Evaluation Board and/or publication in national and international journals.

Every incoming report represents an association between one or more suspected ADRs and one or more suspected drugs, along with patient characteristics. For the analysis of disproportionality a case non-case design is used. The extent to which this association between ADR and suspected drug stands out in respect to its background frequency in the database is calculated using a 'reporting odds ratio' (ROR) as a measure of disproportionality.

Based on the classical 2×2 contingency table, for each association of drug and ADR the four

values are calculated (figure 1). In the figure, cell 'a' represents the number of reports on which the same combination of suspected drug and suspected ADR was mentioned, cell 'b' the number of reports concerning the suspected drug but with other possible ADRs, cell 'c' the number of reports concerning the suspected ADR associated with other drugs, and cell 'd' the number of reports concerning other drugs associated with other ADRs. A report on one ADR and two suspected drugs is counted as one report (concerning the drug under investigation). In the event that two or more suspected ADRs are being reported, the report is also counted only once (for the suspected ADR under investigation). The ROR is defined as the product of the exposure odds among the cases in respect to the exposure odds among the non-cases and is calculated by (equation 1).

$$\text{ROR} = \frac{a \times d}{b \times c}$$

The 95% CI is calculated by (equation 2):

$$95\%\,\text{CI} = e^{[\ln(\text{ROR}) \pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}]}$$

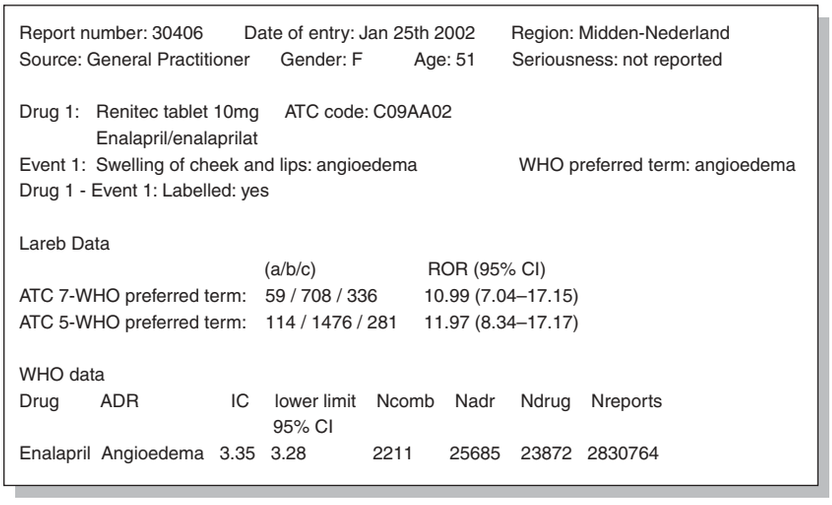
The CI is calculated two-sided and used to get an impression of the actual strength of the signal. This case non-case design is the basis of quantitative signal detection, which is applied in three ways at the Netherlands Pharmacovigilance Centre. Firstly, results of the statistical analysis are used in the traditional case-by-case review. Secondly, for data-mining purposes, a list of associations of ADRs and suspected drugs that are disproportionally present in the database is periodically generated. Finally, on an *ad hoc* basis, quantitative signal detection is used to study signals in more detail, for example, by adjusting for covariates or analysing more complex relationships, such as drug-drug interactions and drug-related syndromes. These three approaches will now be discussed in more detail.

	Reports with the suspected ADR	Reports without the suspected ADR
Reports with the suspected drug	a	b
All other reports	c	d

Fig. 1. A 2 × 2 contingency table for calculating disproportionality. **ADR** = adverse drug reaction.

2. Quantitative Approach as an Aid in the Traditional Case-by-Case Review

In the case-by-case review, the results of the quantitative approach serve as an additional source of information. After a report is received by Lareb, it is assessed by a physician or pharmacist and subsequently stored in an Oracle database. For a first impression of the association, overview forms are compiled, with concise information regarding the reports that will be discussed at weekly assessment meetings. In these meetings every new report is discussed, on average 50–60 reports. Among information regarding age and sex of the patient, the suspected drug, suspected medication and the source of the report (either physician or pharmacist), the results of the quantitative analysis are presented. RORs are calculated using two different approaches. First, unadjusted RORs are calculated based on the number of reports with the generic compound of the suspected drug (expressed as the entire ATC code) and the suspected ADR. In addition, a second unadjusted ROR is calculated based on the first five positions of the ATC code, representing the extent of disproportionality for chemically related sub-



Report number: 30406 Date of entry: Jan 25th 2002 Region: Midden-Nederland
Source: General Practitioner Gender: F Age: 51 Seriousness: not reported

Drug 1: Renitec tablet 10mg ATC code: C09AA02
Enalapril/enalaprilat
Event 1: Swelling of cheek and lips: angioedema WHO preferred term: angioedema
Drug 1 - Event 1: Labelled: yes

Lareb Data

	(a/b/c)	ROR (95% CI)
ATC 7-WHO preferred term:	59 / 708 / 336	10.99 (7.04–17.15)
ATC 5-WHO preferred term:	114 / 1476 / 281	11.97 (8.34–17.17)

WHO data

Drug	ADR	IC	lower limit 95% CI	Ncomb	Nadr	Ndrug	Nreports
Enalapril	Angioedema	3.35	3.28	2211	25685	23872	2830764

Fig. 2. An example of an overview form used in the assessment meetings. Two reporting odds ratios (RORs) with corresponding numbers of cells a, b and c of the contingency table are shown. **ADR** = adverse drug reaction; **IC** = information component; **Ncomb** = number of records concerning the suspected drug and ADR; **Nadr** = number of ADRs; **Ndrug** = number of drugs; **Nreports** = total number of reports in the Uppsala Monitoring Centre database.

stances, for instance groups of β-blocking agents or ACE inhibitors. For calculation of RORs and confidence intervals, the Oracle database is linked to a Microsoft Access database and calculations are carried out in the latter. If desired, correction for various covariates, such as age, sex, year of reporting or source of the reports is possible in an additional logistic regression analysis, but is not carried out routinely for the case-by-case analysis. Since only a minority of the reports (0.6%) have missing data on sex or age,[17] and differential misclassification is not likely to occur in respect to the reports with these missing covariates, these reports are not taken into account in a logistic regression analysis.

Figure 2 shows an example of an overview form as it is used for a first impression of the reports in the weekly assessment meetings. Next to data concerning patient characteristics, such as age and sex, the results of the quantitative signal detection of the Lareb database are shown. In this example, the first ROR shows the extent to which enalapril is associated with reports of angioedema. This ROR is statistically significant (11.0 [95% CI 7.0–17.2]), implying that angioedema is significantly associated with enalapril in reference to other reports in the database. The second ROR refers to the association between angioedema and the total group of ACE inhibitors. Also, this ROR is statistically significant (12.0 [95% CI 8.3–17.2]), implying that ACE inhibitors in general are associated with this ADR.

For a more detailed discussion of the reports, additional information is generated. It concerns detailed information on the original reports sent in by the reporting physicians and pharmacists, information regarding the association in literature and concomitant medication used by the patient.

Next to results of calculations based on the data set of the Netherlands Pharmacovigilance Centre, the results of the quantitative signal detection on the data set of the UMC are available. As a measure of disproportionality, the information component is provided.[11] On a quarterly basis, quantitative data of each drug-ADR combination that was received by the UMC are sent to national pharmacovigilance centres. This database, containing summarised information regarding combinations of drugs and

ADRs, which is expressed as the ATC code and the preferred term of the WHO ADR-terminology, respectively, is linked with the Lareb database. In this way quantitative data from a second source provide additional insight on the existence of possible signals. Since the database of the UMC also contains reports of the Netherlands Pharmacovigilance Centre, some reports may be filed in both databases. However, the proportion of Lareb reports in this WHO database is relatively small (approximately 30 000) compared with the total number of reports in the WHO database (over 2 million). For this reason, it is unlikely that the number of Dutch reports will have a great influence on calculations based on the data set of the UMC, which implies that the two sources of information can be regarded as independent of each other.

3. Quantitative Signal Detection as a Data-Mining Tool

Quantitative signal detection can also be used more actively as a data-mining tool. By screening the database, overviews with disproportionate associations can be generated. A disproportionate association may represent a signal and therefore should be analysed in more detail. This approach can be used to monitor for disproportionate associations that were not selected by the traditional case-by-case approach. Using this data-mining technique, one or more additional filters can be applied. For example, by filtering the unlabelled cases, a selection can be made with associations that need further follow-up because they may represent unknown ADRs. As an example, associations concerning the occurrence of angioedema in suspected association with various drugs, which were received by Lareb between 1 January 1985 and 1 June 2002, were listed (table I). The associations are sorted by the lower limit of the confidence interval of the ROR, in descending order. In addition to the drug and suspected ADR the numbers of reports in the cells of the aforementioned contingency table are shown as well as whether the association is labelled or unlabelled. As might be expected, angioedema is mainly associated with ACE inhibitors and angiotensin II inhibitors. Applying filters is merely a way of handling the large amount of data. It more or less guides the selection of the cases but does not add in the ability to detect signals.

4. Analysis of More Complex Relations: Drug-Drug Interactions and Drug-Related Syndromes

Generally in signal detection we are interested in the relationship between the patient (characteristics), suspected drug(s) and ADR(s). Most often this

Table I. Example of the data-mining approach; disproportionality, expressed as the reporting odds ratio (ROR) with corresponding 95% CI and the number of reports in cells a, b and c of the contingency table of various combinations of angioedema and reported drugs. In this example, the associations are sorted by the lower limit of the confidence interval in descending order

Suspected drug	Labelled/unlabelled	ROR	95% CI	a	b	c
Enalapril with diuretics	Labelled	56.9	28.9–111.9	15	20	434
Fosinopril	Labelled	27.6	13.7–55.3	11	30	438
Enalapril/enalaprilat	Labelled	11.9	9.1–15.5	73	529	376
Losartan with diuretics	Labelled	21.8	8.0–59.4	5	17	444
Quinapril/quinaprilat	Labelled	13.3	6.2–28.3	8	45	441
Lisinopril	Labelled	9.0	5.7–14.2	22	187	427
Captopril	Labelled	6.3	3.9–10.1	19	231	430
Valsartan	Labelled	8.3	3.5–19.3	6	54	443
Paracetamol (acetaminophen)	Labelled	6.7	3.2–13.9	8	89	441
Losartan	Labelled	5.0	3.1–8.1	19	287	430
Irbesartan	Labelled	6.7	2.7–16.9	5	55	444

refers to one drug and one event. Since a report sent to an SRS contains information about one patient, one or more (suspected) drugs and one or more suspected ADRs, all these factors may be interrelated. If a certain ADR occurs more often than expected in the event that two drugs are used concomitantly, this may indicate the existence of a drug-drug interaction. Similarly, a clustering of two ADRs may indicate the existence of a drug-related syndrome, i.e. the clustering of two or more symptoms. These complex relationships may not always be transparent and therefore often require statistical analysis. An example is the clustering between drugs in the search for possible drug-drug interactions. Logistic regression analysis can be used to analyse this clustering by introducing interaction terms in the logistic model.[18,19] Another example is the analysis of syndromes, in which, similar to the detection of drug-drug interactions, the clustering of suspected ADRs is analysed.[17] These analyses can also be used for the routine screening of the database for drug-drug interactions and syndromes. After all, for each combination of two drugs it can be calculated whether the number of observed ADRs exceeds the number of expected ADRs (figure 3a), which may represent a possible drug-drug interaction.

Although the reporting health professional usually makes a distinction between suspected and concomitant medication, in the analysis of drug-drug interactions, all drugs are used in the calculations. These calculations can be carried out for the various ADRs in the database, represented by the cross-sections in figure 3a. Similar to the detection of drug-drug interactions, this approach can also be applied to screen the database for drug-related syndromes. In this approach, the calculations in the cross-sections concern the combination of two ADRs for a certain drug, which is reported more frequently than expected (figure 3b).

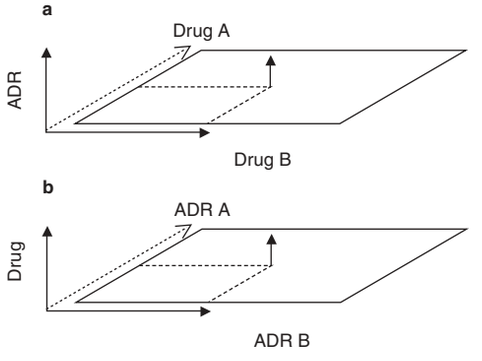


Fig. 3. Data-mining approach for (**a**) the detection of drug-drug interactions and (**b**) drug-related syndromes. **ADR** = adverse drug reaction.

5. The Place of Quantitative Signal Detection

Case reports or case series are highly sensitive in picking up qualitative signals. On the other hand, they are limited in their ability to provide quantitative information. With current information technology, calculations can be made in a short time span and, additionally, adjustments for various covariates, such as age, sex and concomitant medication, can be made. However, the major disadvantage of a quantitative approach is the fact that clinical information can be taken into account only to a limited extent. When used as a data-mining tool, it should be considered as a filtering mechanism to focus attention to associations that may represent true signals. Also, for the analysis of possible signals resulting from a case-by-case analysis, it provides additional information. Since not all ADRs are reported, the data set of an SRS does not necessarily constitute a valid representation of the ADRs occurring in daily practice. In other words, a thoughtful interpretation will remain a necessary next step in the detection and analysis of signals.

At the Netherlands Pharmacovigilance Foundation, the ROR is used to analyse the extent of disproportionality, but several other approaches for calculation of the extent of disproportionality are currently available. Each has its own advantages and disadvantages for applicability in different situa-

tions. In general, the results of the approaches do not essentially differ if more than three reports are included.[20]

Data originating from the quantitative approach appeared to be an important factor contributing to the selection and dissemination of possible signals originating from the SRS maintained by the Netherlands Pharmacovigilance Foundation. In a case control design, all signals (n = 42) disseminated to the Medicines Evaluation Board from the second quarter of 1997 until the third quarter of 2000, which could be expressed as a combination of a single ATC code and a single WHO preferred term, were included. The influence of various factors was studied, such as whether the ADR or drug was new, the strength of the association, the seriousness of the reaction and the documentation of the reports. Multivariate analysis showed that the presence of a 'serious report' (odds ratio [OR] 3.8, 95% CI 1.3–11), a WHO 'critical term' (OR 4.7, 95% CI 1.8–13), the ADR being unlabelled (OR 6.1, 95% CI 2.3–16) and the presence of a disproportionate association, (OR 3.5, 95% CI 1.4–8.4) were all independently associated with signal selection. This study showed that selection of signals appeared to be based not only on qualitative, but also on quantitative aspects.[21]

In quantitative signal detection, the association between various factors is expressed as a point estimate with corresponding confidence interval. This information should not be considered as having an exact meaning, like the incidence of the ADR, but rather as a tool that facilitates the interpretation of the data in the context of other reports and cofactors in the database. By calculating a measure of disproportionality, like the ROR, the frequency of an ADR associated with a certain drug is being compared with the other reports in the database. The rationale for using this approach is that the composition of different types of reactions in the data set of an SRS is relatively constant.[5] Other reports in the database are being used as a measure of the 'background incidence' of the relevant events and are commonly used for reference purposes. Although this is a large group, which has the advantage that smaller confidence intervals can be calculated, its composition is also heterogeneous. If, for instance, liver function disorders are over-represented in a certain pharmacological group, being part of the reference group, the number of ADRs needed for the drug under investigation to yield a statistically significant result will also increase. There is a chance that under these circumstances rare liver function disorders associated with a new drug will be less easily detected. This implies that great care should be taken in choosing the reference group. Especially for pharmaceutical industries that have limited information regarding the reporting of ADRs associated with other drugs, this is an important point to consider. Interpretation of the quantitative results based on data sets of spontaneous reporting systems should be carried out by assessors who are experienced in this field and who have an expert knowledge of the composition of the database.

6. Further Research

An SRS should be considered as a diagnostic tool for health authorities, health professionals and the industry; the results can be used to weigh benefit and safety of the drugs involved. A balance must be found between the sensitivity, specificity and false-positive and false-negative signals in order to establish an optimal signal-to-noise ratio. Therefore, a point to consider is the validation of quantitative approaches. Since there is no gold standard concerning the various measures of disproportionality, validation studies are few and far between. The aforementioned BCPNN analysis of the WHO, however, has recently been validated.[22] Validation studies may be hampered by the fact that, as yet, no true gold standard is available. Additionally, the validity of a quantitative approach strongly depends on the

data set to which it is applied. Therefore, validation of the quantitative signal detection within the Lareb data set and those of other SRSs needs to be corroborated by additional, more elaborate studies. One of the possible approaches could be comparison with case reports of new ADRs published in the literature. However, publication of case reports in national and international journals is not primarily intended to give an early warning.[22] This implies that the goals of publication and signal detection in an SRS differ, which hampers the validation process. Another possibility would be setting up an expert panel that is to decide whether the associations reported do indeed represent possible signals. The decisions of this panel could subsequently be used as the validation standard.

The quantitative analyses of the data sets of SRSs give an impression about the occurrence of ADRs within the population of patients experiencing an ADR during the use of a certain drug. Nevertheless, the implementation of data on drug utilisation also would be useful to correct for the number of prescriptions of the drugs involved.

In the majority of reports sent to the Netherlands Pharmacovigilance Foundation information on concomitant drug use is included. For the analysis of associations between ADR(s) and drugs, and for the analysis of drug-related syndromes, however, only the suspected medication is used. If we were to include the concomitant medication in our analyses, we might yield different results. This approach was, for instance, used by Moore et al. in their analysis of the possible association between hypoglycaemia and the use of ACE inhibitors.[23] The differences of these two approaches should be studied in more detail.

The extent to which clinical information can be taken into account is limited in the current method of quantitative signal detection. At present, clinical information first has to be coded, before statistical analyses can be carried out. In the classical, empirical assessment methods, however, clinical information has a more prominent place. To improve the signal detection process, integration of clinical details in the quantitative approach is recommended.

7. Conclusion

Finney[24] stated that the essence in ADR monitoring is to collect facts that individually tell little but that collectively form a fabric of clues to drug dangers. Subsequently, an intelligent interpretation is required for combining these various aspects to draw a conclusion on a possible relationship between suspected drug and ADR. Bringing together information from different sources, therefore, is of great benefit in the analysing process. The results of a quantitative approach should be considered as information that should be interpreted in combination with other sources of information, such as the clinical information and information from literature. From this line of argument, it emerges that an association that is not disproportionately present in the database still can represent a true signal, while an association that is disproportionately present may not necessarily represent a true signal. Human analysis and interpretation of the data is still the decisive factor of the signal detection process. In The Netherlands, quantitative signal detection has been successfully used on a relatively small data set in recent years and has been implemented in the routine analysis.

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