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Use of measures of disproportionality in pharmacovigilance

Belamalem souad[1]*, Khadmaoui Abderazzak[1], Tailibi Ismail[2], Benkirane Rajae[2], Soulaymani Bencheikh-Rachida[2], Soulaymani Abdelmajid[1]

[1]Genetics and Biometry Laboratory, Faculty of Science, University IbnTofail, Kenitra, (MOROCCO)

[2]Moroccan Anti Poison and Pharmacovigilance Center, Rabat 10000, (MOROCCO)

E-mail : souad-1234@hotmail.fr

ABSTRACT

Pharmacovigilance ensure employment drug safety and consists in collect and manage data on the use of drug and to exploit these data, to detect unknown effects after postmarketing. The primary goal of spontaneous reporting systems related to health products is the detection of unknown adverse reactions or signal detection for which a correlation between the appearance of an adverse effect and a medication. Different disproportional methods are used in pharmacovigilance to generate potential signals, among which, we find : the Proportional reporting ratio (PRR) associated with the chi-square test, the Report Odds Ratio (ROR), the Yules'Q, the Bayesian Confidence Propagation Neural Network (BCPNN) or Information Component (IC) These sophisticated methods are used in advanced countries at the moment.

INTRODUCTION

There have been several examples of patients being harmed by prescribed marketed medicines, the thalidomide tragedy being the paradigm case[1]. Recently, the decisions to prescribe and administer medications are influenced by the associated risks of adverse drug reactions. An adverse drug reaction (ADR) is defined as any harm associated with the use of given medications at a normal dosage during a normal use. ADR may occur following either a single dose or prolonged administration of a drug or result from the combination of two or more drugs[2,3].

Modern medicine has changed the way in which diseases are managed and controlled. However, despite of all their benefits, evidence continues to mount that adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death[4].

Drug safety and pharmacovigilance remains a dynamic clinical and scientific discipline. Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem'[4] it plays a vital role in ensuring that doctors, together with the patient, have enough information to make a decision when it comes to choosing a drug for treatment[5,6].

This paper discusses analytical approaches of signal detecetion methods such as the frequentist approaches and The Bayesian based approaches.

MATERIALS AND METHODS

Source

Signal detection is made from spontaneous reports notified to the pharmacovigilance center by healthcare professional, pharmaceutic industry or the public. For

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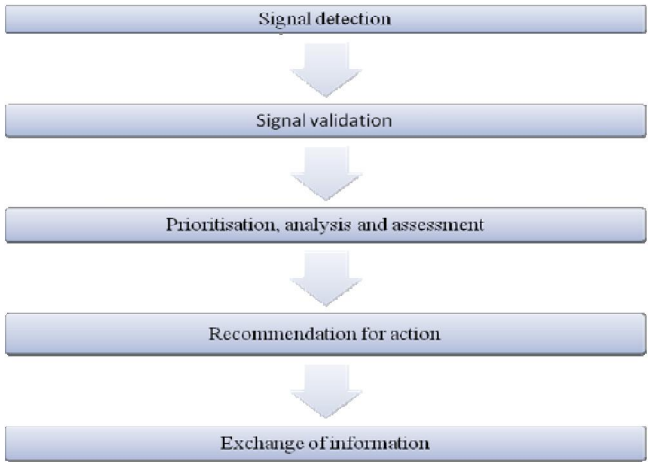
data harmonization, the adverse reactions were coded into WHO art terminology prefered terms and for the drugs we used the International Nonproprietary Name.

The signal is defined as follows in Pharmacovigilance: «Information that arises from one or multiple sources, which suggest a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verily action»[7]. Procedure followed for Signal Detection which is a set of activities to determine based on various data sources whether there are new/changed risks associated with active substances/medicinal products in five steps :



Disproportional methods

Practically, each submitted safety report may involve several suspected drugs and several observed events, leading to J (total number of) drugs and I (total number of) events mentioned at least once in a report. The association measures provided by the different SD data mining methods are calculated by 2 by 2 contingency table (TABLE 1).

These are the frequency or relative frequency of a particular drug–event pair. The signal would be considered significant if the statistics from different calculations such as Proportional Reporting Ratio (PRR), to evaluate the disproportionality for each couple, the statistical significance level was set at PRR > 2, chi square >4, the number of individual cases >3, for the Reporting Odds Ratio (ROR), if the lower confidence (IC to 95 %) limit of the ROR is ≥1, it detects a potential signal or Yule's Q to generate de signal if the lower confidence (IC to 95 %) limit of the Yule's Q>0.

Moreover, Bayesian Confidence Propagation Neural Network (BCPNN) analysis was proposed based on Bayesian logic where the relation between the prior and posterior probability was expressed as the "information component (IC)". The IC given by the BCPNN is applied by the WHO Uppsala Monitoring Center (UMC). This method generates a signal when

TABLE 1: Two by two table for the adverse drug-event pair

	adverse event j	other adverse event $\bar{j}$	Total
drug (i)	n_{ij}	$n_{i\bar{j}}$	ni.
other drugs $\bar{i}$	$n_{\bar{i}j}$	$n_{\bar{i}\bar{j}}$	$n\bar{i}.$
Total	n.j	$n.\bar{j}$	n

n_{ij} :The number of reports involving the drug of interest i and adverse effect of interest j combination

$n_{i\bar{j}}$: Reports of drugs interest with other adverse effect

$n_{\bar{i}j}$: Reports of all other drug s with adverse effect of interest

$n_{\bar{i}\bar{j}}$: Reports of all other adverse effect with the other drugs

the lower confidence (C I to 95 %) limit of the IC is >0.

Findings

(1) Proportional reporting ratio

The PRR is a statistical method used to detect the statistically significant associations for pairs drug / adverse effects.

The approach of performing the calculations of the PRR on the individual case counts instead the number of ADRs has been chosen to keep the independence between the variables used to compute the PRR so that the variance of the PRR will not be underestimated.

The PRR is computed as follows[8]

$$PRR\ (i, j) = nij/ni / n\bar{i}\ j/n\bar{i}.$$

The 95% confidence interval of the PRR

The standard deviation of the natural logarithm of the PRR is estimated based on the following formula:

Var {LnPRR (i, j)}= $1/nij - 1/ni. + 1/n^{-}ij - 1/n\bar{i}.$

The 95% confidence interval for ln(PRR) is then estimated as ln(PRR) ±1.96 Var (LnPRR) and, taking the exponential, the following result is obtained: 95% confidence interval for PRR by the following formula :

$$IC95\%(PRR) = [\exp(Ln\ PRR - 1.96 \times \sqrt{var(LnPRR)} : \exp(LnPRR + 1.96 \times \sqrt{var(LnPRR)}$$

Measures of statistical association are calculated using a chi-squared test with one degree of freedom. If the drug and condition are independent, the expected value of PRR should be 1; a PRR>1 indicates a greater than expected frequency of the report (i,j) in the dataset. When the PRR is displayed with the chi-square statistics, a signal is reported if the PRR is greater to 2, the chi-squared statistic is at least 4 and number of adverse event is at more than 3[8]. Also when the PRR is displayed with its 95% confidence interval, a signal is generated if the lower bound of the 95% confidence interval greater[9].

The Chi-square is a statistic, used in disproportionality analyses. In certain standard query of the chi-square is used as an alternative measure of association between the drug product and the adverse event R based on the following calculation:

$$\text{Chi-Square} = \sum \frac{(Observed - Expected)^2}{(Expected)}$$

(2) Reporting odds ratio (ROR)

The calculation of ROR was similar to that of the PRR method. The same contingency table that was (TABLE 1) prepared for PRR, was also followed in the case of ROR calculations. The ROR was counted as follows:

$$ROR = \mathbf{ROR} = \frac{nij \times n\bar{i}\bar{j}}{n^{-}ij \times ni^{-}j} \quad (10)$$

The logarithm of the ROR of the pair (i, j) is assumed to follow a normal distribution whose variance is estimated from the delta method as follows[11] :

$$Var\ \{LnROR\ (i\ j) = 1/nij + 1/ni\ \bar{j} + 1/n\bar{i}\ j + 1/n\ \bar{i}\bar{j}$$

An association is considered to be disproportionate in the event that the lower limit of the 95% confidence interval was greater than 1.

$$IC = (e)^{Ln\ (ROR \pm 1,96\ (1/nij + 1/ni\ \bar{j} + 1/n\bar{i}\ j + 1/n\ \bar{i}\bar{j})\ 1/2}$$

(3) Yule'S Q

It is a method derived from the Reporting Odds Ratio (OR). It measures the the liaison intensity between two or more qualitative variables using the formula below[8]:

$$Q = (nij \times n\bar{i}\bar{j} - ni\bar{j} \times n\bar{i}j)/(nij \times n\bar{i}\bar{j} + n\bar{i}j \times ni\bar{j})$$

The signal generation criterion proposed by this method is when the lower limit of the confidence interval at 95% is strictly greater than 0. The formula of the confidence interval is represented by the following formula[12]:

$$95\%\ CI = Q - 1,96((\frac{1}{2}(1 - Q^2) \times \sqrt{\frac{1}{nij} + \frac{1}{n\bar{i}j} + \frac{1}{ni\bar{j}} + \frac{1}{n\bar{i}\bar{j}}}$$

(4) The Bayesian confidence propagation neural network (BCPNN)) or information component (IC)

The statistic of interest is based on the Component Information[13] defined for the cell (i, j) (contingency table). The formula used for calculating VigiMine Information Component (IC) is figured as follows:[14].

$$IC(i,j) = \log_2 \frac{nij + 0,5}{\frac{ni. \times n.j}{n} + 0,5}$$

A signal is generated when the lower limit of the 95% CI> 0 as follows :

95 % CI=IC-3.3(nij+0.5)$^{-1/2}$-2(nij+0.5)$^{-3/2}$

- if IC> 0 the probability of the couple {drug/ adverse effect} observed is greater than the expected probability

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- if IC = 0 the probability of the pair {drug/ adverse effect} observed is equal to the expected probability.

DISCUSSION AND CONCLUSION

Drug is a product that aims to prevent, treat or cure diseases, in both physical psychological fields. However, it can also be a source of risks or side effects which may have a variable severity, ranging from mild itching to death of the user. Put on the market after that clinical trials have demonstrated its safety, quality and effectiveness, has to be put under an increased surveillance because it is statistically proven that unknown risks appears when it is used by a large population[15].

For this reason, post-marketing surveillance is aimed at a timely detection of new adverse effects or an increase in the frequency of adverse reactions that are already known to be associated with the drug involved[16].

Statistical methods are used to support the analysis of large volume of ICSRs to identify the signals. The detection of signals was performed in based of individual cases safety reports ICSRs which generates many potential signals. These hypothesis usually leads to quantitative analysis which measure the disproportionality for the signal strenthening. Recently, pharmacovigilance centers devoted considerable efforts for applying and for the use of quantitative methods for signal detection that employs statistical theory to enhance screening databases of spontaneous reports of Adverse drug reactions.

Lot of methodological issues complicate the systematic and comprehensive assessment of the performances of the quantitative methods of signal detection. The lack of gold standard in signal detection is one important obstacle which makes this evaluation difficult to perform[16,17]. Each method has its own advantages and flaws in respect to applicability in different situations and possibilities for implementation[18]. This could be explained by the higher sensitivity and low specificity calculated[19].

Another comparison technique may be used, such as the kappa statistic, but its disadvantage is that it doesn't distinguish between a high sensitivity situation and low specificity, and one of the low sensitivity and high specificity.

These diproportionnal methods should targets the most common diseases like malaria, HIV/AIDS, and tuberculosis. Consequently, large drug safety datasets have been generated which makes it possible to apply statistical data mining[20].

it is important to note that most of the existing methodology for pharmacovigilance involves assessment of association between a drug and adverse drug reactions. However, association does not necessarily imply causation. Intuitively, causation is not only requires correlation but also a counterfactual dependence[21].

We conclude that the use of quantitative measures analysis is a step forward as a signal detection in pharmacovigilance. More research is necessary into the performance of these approaches, especially its predictive value, its sensitivity and specificity.

REFERENCES

[1] L.Calabrese, A.B.Fleischer; Thalidomide: current and potential clinical applications. The American journal of medicine, **108(6)**, 487-495 **(2000)**.

[2] M.Pirmohamed, A.M.Breckenridge, N.R.Kitteringham, B.K.Park; Adverse drug reactions. BMJ., **316(7140)**, **(1998)**.

[3] Edwards I.Ralph et Aronson, K.Jeffrey; Adverse drug reactions: definitions, diagnosis, and management. The Lancet, **356(9237)**, 1255-1259 **(2000)**.

[4] WHO Policy Perspectives on Medicines. Geneva: WHO; Geneva: World Health Organization. Looking at the Pharmacovigilance: ensuring the safe use of medicines. Available from:http://www.whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf., **(2004)**.

[5] P.Biswas, A.Biswas; Setting standards for proactive pharmacovigilance in India: The way forward. Indian J Pharmacol, **39**, 124–8 **(2007)**.

[6] G.Jeetu, G.Anusha; Pharmacovigilance: a worldwide master key for drug safety monitoring. Journal of Young Pharmacists, **2(3)**, 315-320 **(2007)**.

[7] Practical Aspects of Signal Detection in Pharmacovigilance Report of CIOMS Working Group VIII, Geneva, **(2010)**.

[8] S.J.Evans, P.C.Waller, S.Davis; Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.

Review

Pharmacoepidemiol Drug Saf, **10**, 483–486 **(2001)**.

[9] EMEA. Guidelines on the use of statistical signal detection methods in the Eudravigilance data analysis system, **(2006)**.

[10] A.L.Gould; Practical pharmacovigilance analysis strategies. Pharmacoepidemiol. Drug Safety., **12(7)**, 559–574 **(2003)**.

[11] E.Roux, F.Thiessard, A.Fourrier, B.Begaud, P.Tubert-Bitter; Spontaneous reporting system modelling for data mining methods evaluation in pharmacovigilance in AIME Workshop on Intelligent Data Analysis in Medicine and Pharmacology (IDAMAP), Cyprus, Oct. **(2003)**.

[12] E.P.Van Puijenbroek, W.L.Diemont, K.Van Grootheest; Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. Drug Safety, **26(5)**, 293-301 **(2003)**.

[13] A.Bate, M.Lindquist, I.R.Edwards, S.Olsson, R.Orre, A.Lansner et, R.M.De Freitas; A Bayesian neural network method for adverse drug reaction signal generation. European journal of clinical pharmacology, **54(4)**, 315-321 **(1998)**.

[14] G.N.Norén, J.Hopstadius, A.Bate; Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Statistical Methods in Medical Research, **22(1)**, 57–69 **(2011)**.

[15] L.Largenté; Le système de pharmacovigilance canadien en quête d'une réforme en profondeur? Lex Electronica, (Automne/Fall 2013), **18(2)**, **(2013)**.

[16] E.P.VanPuijenbroek, Kees van Grootheest, Willem L.Diemont, Hubert G.M.Leufkens, Antoine C.G.Egberts; Determinants of signal selection in a spontaneous reporting system for adverse drug reactions. Br J Clin Pharmacol, **52(5)**, 579–586 **(2001)**.

[17] J.Almenoff et al.; Perspectives on the use of data mining in pharmacovigilance. Drug Saf:, **28(11)**, 981-1007 **(2005)**.

[18] E.P.Van Puijenbroek, A.Bate, H.G.Leufkens, M.Lindquist, R.Orre, A.C.Egberts; A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions.Pharmacoepidemiology and drug safety, **11(1)**, 3-10 **(2002)**.

[19] European Medicines Agency. Doc. Ref. EMEA/ 106464/2006 rev. 1 London, 26 June **(2008)**.

[20] D.Kajungu, N.Speybroeck; Implementation of Signal Detection Methods in Pharmacovigilance – A Case for their Application to Safety Data from Developing Countries. Ann Biom Biostat, **2(2)**, 1017 **(2015)**.

[21] M.Liu, M.E.Matheny, Y.Hu, H.Xu; Data mining methodologies for pharmacovigilance. ACM SIGKDD Explorations Newsletter, **14(1)**, 35-42 **(2012)**.