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Signal Detection in Pharmacovigilance: An Application of Subjective Bayesian Inference

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Abstract

The present study proposed a new statistical measure to find out the association between Drug-Adverse Drug Reaction (ADR) pair in the Pharmacovigilance system. The study proposed a subjective Bayesian measure corresponding to Proportional Reporting Ratio (PRR) parameter for quantitative signal detection. Classical and Bayesian inference procedure were used in analysis with four Drug-ADR pair as an example. We made prior information by expert opinion. The result of this analysis shows that Bayesian inference is more reliable as compared to classical inference. This study suggests that in case of spontaneous reporting in Pharmacovigilance system subjective Bayesian inference better to applying in case of small sample size.

Keywords: Pharmacovigilance; Signal detection; Bayesian inference; Proportional reporting ratio

Introduction

The goal of Pharmacovigilance is to identify such drug which is responsible for cause of adverse drug reaction and ensuring patient safety by using drugs. The association between certain drug and ADR [1] is identified by certain statistical tools. This identification for certain drug-ADR pair is known as Quantitative Signal detection. It refers to computational or statistical methods used to identify drug-event pairs (higher-order combinations of drugs and events) that occur with disproportionately high frequency in large safety databases. The reason behind using such statistical methods that large size of dataset makes individual case by case assessment impossible when entering cases into the database. For this purpose US-FDA using a tool Emperical Bayes Geometric Mean (EBGM). Uppsala Monitoring Centre for WHO using Information Component(IC) to identify Statistical (Quantitative) Signal. The Italian agency and LAREB (Dutch agency) are using the PRR and Relative Odds Ratio (ROR) for signal detection. In literature there are two types of statistical inference to identify signal, first is Classical approach and second is Bayesian approach. In classical inference we say that parameter is an unknown constant and whatever information is provided by sample is sufficient to make inferences about parameter. The classical method totally depends on sampling distribution of estimator and the sampling distribution is not so easy to obtain if sample size is not too large. In Bayesian estimation we directly deal with probability distribution of unknown parameter to make inferences. In other words Bayesian inference is the process of fitting a stochastic model to an observed data and summarizing the result by a probability distribution on the parameters of the model. EBGM and IC are the Bayesian measure of signal detection while PRR and ROR are the classical measure of signal detection. EBGM and IC are the Bayesian version of Relative Reporting Ratio (RRR), but for PRR and ROR, There is no Bayesian measure exist in literature. The whole world on Pharmacovigilance practice has divided into two parts in statistical signal detection methodology [2]. One part of the world is using the no. of reports on particular drug-ADR pair (e.g. RRR) to find out the signal, and not considered the overall reports in database for signal detection. The remaining world uses the measure which is based on the overall reports of adverse events (PRR & ROR). As we explain above for RRR Bayesian version exist while for PRR and ROR there is no measure of Bayesian platform. So the main concern of this study to develop a Bayesian measure for PRR, which will easily computable and use the advantage of Bayesian theory.

Methodology

In Frequentist or classical inference, parameters (Like PRR) are not repeatable random things but are fixed quantities, which mean that they cannot be considered as random variables. In contrast, in Bayesian inference anything, about which we are uncertain, including the parameter, can be thought of as being a random variable to which one can assign a probability distribution, known specifically as prior distribution. A fundamental feature of the Bayesian approach to statistics is the use of prior information (prior distribution) in addition to the data (sample). A proper Bayesian analysis will always incorporate genuine prior information, which will help to strengthen inferences about the true value of the parameter and ensure that any relevant information about it is not wasted. In Bayesian inference there are two types of prior one is objective prior and another is subjective prior.

Objective Bayesian inference

The Bayesian inference procedure is divided into objective and subjective on the basis of prior selection in Bayesian analysis. If prior information taken such a defined rule and if any one follow the same standard rule then all are find same result e.g. in case of non-informative prior and Jeffrey's prior.

Subjective Bayesian inference

When prior information derives from subjective point of view such that prior selection varies from person to person's choice for same analysis.

Present study used subjective Bayesian prior for PRR .This study applies two statistical views on PRR. First Classical view of calculation of PRR and Second view is subjective Bayesian inference on PRR. PRR is defined by following way: PRR (Proportional Relative Risk): It is a simple measure which gives how many times risk of ADR higher in drug exposed category as compare to drug unexposed category (Table 1).

	ADR+	ADR-	All ADR
Drug+	a	b	M+
Drug-	c	d	M-
All Drug	N+	N-	T

Table 1: ADR proportional relative risk.

$$PRR = \frac{Risk\ of\ adverse\ event\ in\ drug\ \text{exposed}\ category}{Risk\ of\ adverse\ event\ in\ drug\ \text{unexposed}\ category} = \frac{p_1}{p_2} = \frac{\frac{a}{M+}}{\frac{c}{M-}}$$

$$PRR = \frac{a * M-}{C * M+}$$

The distribution of PRR is not accessible, so by taking distribution of Log (PRR) which is approximate normal distribution. We can find the 95% confidence interval (CI) for PRR in case of classical inference procedure.

$$CI^{PRR}_{Lower/Upper} = PRR * e^{\pm 1.96 * \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{M+} - \frac{1}{M-}}}$$

The above mentioned description of PRR is based on the classical statistics. Now we can change it in Bayesian setup for setting prior for the and. So we set the prior distribution for the and as uniform distribution which is varying from 0 to 0.1. The prior elicitation is taken by experts' opinions which have the experienced in the drug use and their consequences. They all are told that these pair have rare chance for occurring and literature have small information on such drug-ADR pairs. So we supposed that the incidence of these ADR have not greater than 10%, that is why we take a prior information which shows that ADR have probability of occurrence not more than 10%. The and taken as to follow binomial distribution (current knowledge). The prior distribution will combine with current knowledge by using Bayesian theorem and on this combination we will find the posterior distribution for the and If one may want to perform this analysis for more than one drug and ADR combination then the use of multinomial drichelete setup for the analysis will be appropriate choice.

The Bayesian methodology is easily performed using winBUGS Software [3]. The Bayesian methodology works in following way.

Posterior distribution of selected parameter

Prior distribution (Prior knowledge)* Likelihood (Current knowledge coming from the data).

For describing the proposed methodology four drug–ADR pair were taken from the Pharmacovigilance database of India. The selected drug-ADR pair are given in Table 2.

Sr. No.	Drug	ADR	Uses of Drug
1	Piperacillin Sodium and Tazobactam Sodium	Bronchospam	Systematic Antiboitic for bacterial infection.
2	Ceftriaxone	Peripheral Neuropathy	For the treatment of lower respiratory tract infection
3	Sodium Valproate	Slurred speech	Indicated in the management of simple and complex absence seizures, myoclonic and generalised tonic-clonic (grand-mal) seizures.
4	Paracetamol	Steven Johnson syndrome	Analgesic-antipyretic

Table 2: Description of drug-ADR pairs.

Piperacillin Sodium and Tazobactam Sodium: Piperacillin, a broad spectrum, semisynthetic penicillin active against many Gram positive and Gram negative aerobic and anaerobic bacteria, exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulfone, is a potent inhibitor of many beta-lactamases, including the plasmid and chromosomally mediated enzymes that commonly cause resistance to penicillins. The presence of tazobactam in the piperacillin/tazobactam formulation enhances and extends the antibiotic spectrum of piperacillin to include many beta-lactamase producing bacteria normally resistant to it. Thus piperacillin/tazobactam combines the properties of a broad spectrum antibiotic and a beta-lactamase inhibitor [4].

Ceftriaxone is a third generation cephalosporin antibiotic that has a broad antibacterial spectrum. It works by interfering with the formation of the bacteria's cell wall so that the wall ruptures, resulting in the death of the bacteria. Currently, it is the most reliable and fastest acting bactericidal drug for enteric fever [5].

Sodium Valproate is a branched chain aliphatic carboxylic acid with a broad spectrum anticonvulsant action. It is very effective against absence seizures and is often preferred to ethosuximide when the patient has concomitant generalized tonic-clonic attacks. It is unique

in its ability to control certain types of myoclonic seizures; in some cases the effect is very dramatic. The drug is effective in tonic-clonic seizures, especially those that are primarily generalized [5].

Paracetamol (acetaminophen) is the deethylated active metabolite of phenacetin. It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on Cyclooxygenase in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and anti inflammatory actions is its inability to inhibit Cyclooxygenase in the presence of peroxides which are generated at sites of inflammation, but are not present in the brain. The ability of paracetamol to inhibit Cyclooxygenase-3 (an isoenzyme so far located in dog brain) could also account for its analgesic antipyretic action [5].

Result

Statistical Data Analysis of selected Drug-ADR combination according to proposed methodology has performed and result of analysis is mentioned in Table 3. WinBUGS and Microsoft Excel are used to perform such analysis.

Pair	PRR		LB(PRR)		UB(PRR)	
	Classical	Bayesian	Classical	Bayesian	Classical	Bayesian
1	24.02	25.98	11.58	11.76	49.81	42.07
2	31.24	31.61	24.35	24.39	40.09	40.03
3	0.29	0.43	0.07	0.09	1.15	1.03
4	1.84	2.30	0.69	0.75	4.92	4.70

Table 3: Comparison between classical and Bayesian inference.

Table 3 shows that point estimate for PRR as well as their confidence interval in form of Lower Bound (LB) and Upper Bound (UB), Study is used these term because in case of Bayesian analysis we calculate highest posterior density interval in place of confidence interval which is the replacement of confidence interval. Although the inferential pattern in classical and Bayesian setup is quite different but in nut shell the confidence interval and HPD interval both are talking about the reliability of point estimate i.e., as short as this interval become the estimate is more reliable or precise.

In all four pairs the range of PRR estimate are short in case of Bayesian inference as compared to the classical inference. If we see the point estimate of PRR as well as LB of PRR in case of Bayesian and classical inference, they are nearly similar. The interval of PRR defined the significant of PRR .If range of PRR (LB-UB) contains the value 1 then PRR is insignificant for drawing the conclusion. For pair 1 and 2, the value of PRR is significant for conclusion, but in case of pair 3 and 4 it is not significant. If we are taking pair one i.e., Piperacillin Sodium and Tazobactam Sodium–Bronchospam, then the value of PRR 24.02 (classical) shows that the risk of Bronchospam is 24 times higher in case of Piperacillin Sodium and Tazobactam Sodium consumption as compared to consumption of other drugs on the basis of ICSR in Indian database. The interpretation of PRR is similar in both cases in classical as well as in Bayesian inference.

Discussion and Conclusion

In Pharmacovigilance, signal detection is crucial issue and it remains unsolvable till at present due to shortage of data and the representation of data. The various statistical tools are available for signal detection. Some methods are working on classical theory and some on Bayesian theory. If we are talking about classical method like PRR then the confidence intervals are very high due to small number of drug-ADR pair. In Bayesian method like IC the prior knowledge would also taken with current data so the signal estimate become more reliable, but IC value taken log function for calculation of estimates. Another drawback of this method that it is quite complicated and one cannot use this without computer generated programme with complex programming syntax [6]. So for resolving these issues we proposed current methodology. The current methodology not used the log function and easy to calculate. The current method narrow down the confidence interval it is due to the strong prior knowledge. The LB is not change here because we have not taken any lower limit for parameter in prior knowledge and we just fixed it with lower limit of parameter.

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