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Sequence Symmetry Analysis and Disproportionality Analyses: What Percentage of Adverse Drug Reaction do they Signal?

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Abstract

Background: Sequence Symmetry Analysis (SSA) is a method to detect Adverse Event (AE) signals using administrative claims data. Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) are methods to detect AE signals using spontaneous reporting data. The proportion of AEs detected by all four methods is unknown.

Objective: To determine sensitivity, specificity and predictive values of SSA, PRR, ROR and BCPNN for a set of medicine-AE pairs.

Methods: All AEs identified in published Randomised Controlled Trials (RCTs) and Product Information (PI) were extracted for 19 medicines. Gold standard positive AEs were events identified in powered RCTs and gold standard negative AEs were events not listed in the PI for that medicine or any other medicines in the class. SSA was performed for each medicine-AE pairs using Australian Goverrnment Department of Veterans Affairs' data, while the PRR, ROR and BCPNN, was calculated using the Food and Drug Administration Adverse Events Reporting System data.

Results: A total of 157 medicine-AE pairs (43 positive and 114 negative) were identified and tested. SSA, PRR, ROR and BCPNN had a sensitivity of 65%, 19%, 49% and 51% respectively. Specificities across all methods were similar; 89%-97%. Thirty percent of true positive pairs were detected by all methods. SSA detected an additional 35% different true positive pairs while PRR, ROR and BCPNN methods detected an additional 21% different true positive pairs.

Conclusions: Using the combination of signalling methods and data sources, more adverse drug reactions can be detected and could potentially strengthen the safety surveillance of post-marketing medicine.

Keywords: Sequence symmetry analysis; Disproportionality analysis; Adverse drug reaction detection

Introduction

Post-marketing surveillance systems rely on spontaneous reporting databases maintained by health regulators to identify safety issues arising from medicines once they are marketed. Quantitative safety signal detection methods such as Proportional Reporting ratio (PRR), Reporting Odds Ratio (ROR), Bayesian Confidence Propagation Neural Network (BCPNN), and empirical Bayesian technique are applied to spontaneous reporting data to identify safety signals [1-3]. These methods have been adopted as standard quantitative methods by many pharmaco-surveillance centres to screen for safety signals of medicines [2-5]. Studies have validated these methods and showed that the methods have low to moderate sensitivity to detect adverse drug reaction (ADR) signals, ranging between 28% to 56%, while the specificity of the methods ranged from 82% to 95% [6-8].

Voluntary reporting systems have contributed to early identification of previously unknown ADRs, such as flucoxacillin-induced hepatitis and cisapride-induced cardiac arrhythmia [9-11]. There are limitations associated with spontaneous reports such as under-reporting, uncertain quality of information in adverse event reports and inability to identify the incidence of adverse events in voluntary systems [12-13]. Administrative claims databases have the potential to complement spontaneous reports. The administrative claims data have wide population coverage and routine collection of data on exposures (prescription medicines) and outcomes (for an example hospitalisation diagnosis) and are usually stored electronically [14-16]. The advantages of claims data may enable detection of medicine adverse event signals because complete capture of exposures and outcomes can be investigated.

Sequence symmetry analysis (SSA) has been used in previous studies to investigate adverse events associated with medicines using administrative claims data [17-26]. A previous study showed SSA has moderate sensitivity (61%) and high specificity (94%) [27]. The aim of this study was to assess the extent of SSA method for ADR detection in administrative claims database compared to existing standard quantitative methods in spontaneous reporting databases (PRR, ROR and BCPNN) for the same set of medicine-adverse event pairs.

Methods

This study was approved by the Human Research Ethics Committee,

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University of South Australia and the Department of Veterans' Affairs Research Ethics Committee.

Selection and identification of tested medicines and gold standard adverse events

The selection of medicine and adverse event have been reported elsewhere [27]. Adverse events were considered gold standard positive events if the event was statistically significant in adequately powered randomized clinical trials. Gold standard negative events were those not listed as an adverse event in the product information for the medicine or any other medicine in the class. One hundred and fifty seven medicine-adverse event pairs for 19 medicines were evaluated. The list of tested medicines-adverse event pairs can be found in Appendix A.

Study 1-ADR detection in spontaneous reporting database

Spontaneous reporting database: The United States Food and Drug Administration Adverse Events Reporting System (FAERS) database is a computerised spontaneous reporting database of medicines and adverse events that was used in this study [28]. The database is designed to support the FDA's post-marketing safety surveillance program for medicine and therapeutic products. In 2010, the majority of the reports (62%) were voluntarily reported by health professionals and consumers in the United States [29]. Other countries (32%) also contributed reports to the database [29]. All reported adverse events in the database are coded using a standardised, international terminology, MedDRA (Medical Dictionary for Regulatory Activities). Medicine names are coded using either generic names or trade names.

The FAERS raw data from 2004 and onwards were downloaded from the FDA website [30]. All reports received by the FDA between January 2004 until July 2010 was used in this analysis. Duplicate adverse event reports were excluded. Reports with missing information for adverse events or medicine name were also excluded. After excluding duplicates and cases with missing data, the total number of medicine-adverse event pairs for final analysis was 10,804,054. Because the FAERS data consist of reports around the world, all trade names of the tested medicines were identified using Martindale [31]. Extensive spelling checks for each medicine were applied. For the adverse events, all terms under the Preferred Term of MedDRA were searched. Keywords of the adverse events term were also used to identify the events in the database. The preferred terms used for adverse events are listed in Appendix B.

Identification of ADR in spontaneous reporting database: Three standard pharmaco-surveillance methods in spontaneous reporting databases; Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN), were applied for each medicine-adverse event pairs in the FAERS database. These methods have been described in detail previously [1-3,5]. These methods are disproportionality analyses based on 2×2 tables as shown in Table 1. Table 2 shows the information used to support the calculation for all three methods. Signals are considered to be present when signal criteria for the three methods are met (Table 2). These signal criteria have been used by medicine regulatory agencies in the United Kingdom and European countries [2,3-5]. Counts of drug-event pairs were used as the unit of analysis in calculating the PRR and ROR statistics. For the BCPNN calculation, we used counts of reports

Medicines	Specific Adverse events	All other adverse events	Total
Specific medicine	A	B	A+B
All other medicines	C	D	C+D

Table 1: 2×2 table of the disproportionality analysis of PRR, ROR and BCPNN.

Method	Regulatory agencies	Information used	Criteria for signal detection
PRR	Australia, United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), Italian Regulatory Agency, European Medicine Agency.	[A/(A+B))/(C/(C+D)]	PRR ≥ 2, A ≥ 3, $x^2 \geq 4$
ROR	Netherlands Pharmacovigilance Foundation Lareb.	(A/B)/(C/D)	Lower limit of 95% CI ≥ 1
BCPNN	Uppsala Monitoring Centre (World Health Organization (WHO) Vigibase).	Log2 [p (x,y)/p(x)p(y)]	Lower limit of 95% CI>0

CI=Confidence interval; **A**=case reports of medicine associated with adverse events; **x^2**= chi-square; **p(x)**=probability of medicine 'x' reported on database, **p(y)**=probability of adverse event 'y' reported on the database, **p(x,y)**=probability of medicine 'x'- adverse event 'y' combination reported on the database

Table 2: Pharmaco-surveillance methods used by regulatory agencies, information used to generate signal and the threshold for ADR signal.

[1]. Sensitivity, specificity and predictive values were calculated based on the 2×2 table [32]. All analyses were carried out using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA; www.sas.com).

Study 2-ADR detection in administrative claims database

Administrative claims database: Administrative claims data from the Australian Government Department of Veterans' Affairs (DVA) was used. The DVA database contains information on all medicines and healthcare utilisation by veterans for which DVA pays a subsidy. This includes data for all medicines dispensed on the Pharmaceutical Benefit Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS) as well as hospitalisations, for a treatment population of 250,000 veterans [33]. Medicines are coded according to the World Health Organization (WHO) anatomical and therapeutic chemical (ATC) classification [34] and the Schedule of Pharmaceutical Benefits item codes [35]. Hospitalisations are coded according to the WHO international classification of disease, 10th revision (ICD-10) Australian modification [36].

Identification of ADR in administrative claims database: Sequence symmetry analysis (SSA) was undertaken for each medicine-adverse event pair within the DVA database. Prescription supply and hospitalisation records between 1 January 2000 and 31 December 2010 were used. SSA has been described in detail previously [24]. Briefly, sequence symmetry analysis determines asymmetry in the sequence of dispensing between medicine and indicator of adverse event within a given time window. The indicator of adverse event can be either a medicine used to treat the adverse event or hospitalisation that would describe the event. The indicators used for adverse events in this study are listed in Appendix C. The sequence ratio is robust to confounders that are stable over time. However, the SSA may be affected by prescribing or event trends overtime. To adjust for the trend, a null effect sequence ratio is calculated for prescription of investigated medicines dispensed within the time window limit before and after the indicator medicines dispensed based on the total exposed DVA population [24]. This ratio estimates the sequence ratio that might be expected due to the trends in medicine use under the assumption that the index medicine and the indicator are unrelated [24]. An adjusted sequence ratio (ASR) is obtained by dividing the crude sequence ratio by the null effect ratio [24] and 95% confidence intervals (CI) were calculated [37]. A signal is considered to be present when the lower limit of the 95% CI is one or more. Sensitivity, specificity and predictive values were calculated

based on the 2×2 table [32]. All analyses were carried out using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA; www.sas.com).

ADR detection in spontaneous reporting database and administrative claims database

Descriptive statistics were undertaken to compare detection of medicine-ADR pairs when using any of the four methods; PRR, ROR, BCPNN, and SSA.

Results

Study 1-ADR detection in spontaneous reporting database

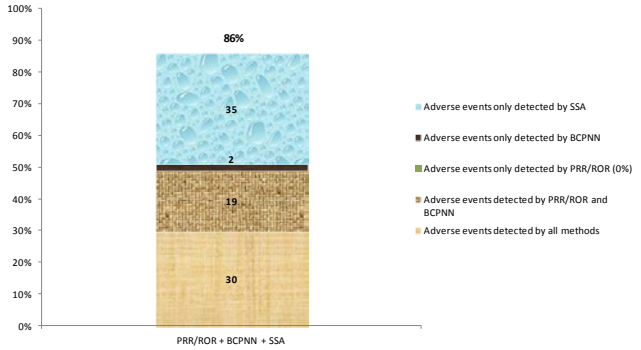
Bayesian Confidence Propagation Neural Network (BCPNN) had higher sensitivity (51%) than PRR (19%) but similar to ROR (49%) (Table 3). Specificity, and predictive values across all disproportionality methods were similar (specificity: 89%-97%, positive predictive values: 65%-73%), negative predictive values: 76%-83% (Table 3)).

Study 2-ADR detection in administrative claims database

Sequence symmetry analysis (SSA) had 65% sensitivity and 90% specificity to detect ADRs (Table 3). Positive and negative predictive values were 72% and 87% respectively (Table 3).

Methods	Proportional reporting ratio (PRR)	Reporting odds ratio (ROR)	Bayesian Confidence Propagation Neural Network (BCPNN)	Sequence Symmetry Analysis (SSA)
Databases	FDA spontaneous reporting database	FDA spontaneous reporting database	FDA spontaneous reporting database	DVA administrative claims database
Signalling criteria	PRR ≥ 2, a ≥ 3, x^2 ≥ 4	Lower 95% CI ≥ 1	IC 95% CI>0	Lower 95% CI ≥ 1
Sensitivity (%)	19	49	51	65
Specificity (%)	97	92	89	90
Positive predictive value (%)	73	70	65	72
Negative predicitive value (%)	76	83	83	87

Table 3: Sensitivity, specificity and predictive values results for SSA, PRR, ROR and BCPNN.



PRR: Proportional Reporting Ratio; **ROR:** Reporting Odds Ratio; **BCPNN:** Bayesian Confidence Propagation Neural Network; **SSA:** Sequence Symmetry Analysis

Figure 1: Combination of all signalling methods to detect true positive events.

ADR detection in spontaneous reporting database and administrative claims database

When using any of the four methods, 86% of true positive adverse events were detected (Figure 1). Thirty percent of true positive pairs were detected by all methods (PRR, ROR, BCPNN and SSA) (Figure 1). SSA detected an additional 35% true positive medicine-adverse event pairs that were not detected by other methods. PRR, ROR and BCPNN detected an additional 21% true positive association that were not detected by SSA.

Discussion

The findings of this study suggest that use of a combination signalling methods to detect adverse drug reactions (SSA in administrative claims database and PRR, ROR, BCPNN in spontaneous reporting database) is better than any of the four methods alone to detect adverse drug reactions. This study also has demonstrated that for a list of medicine-adverse event pairs, SSA has higher sensitivity compared to other signal detection algorithms using spontaneous reporting data (Table 1). Although the PRR had slightly higher specificity (97%) compared to SSA (90%), PRR had the lowest sensitivity (19%) to detect the tested medicine-adverse pairs. This study suggests that SSA is a potential complementary tool to enhance current pharmaco-surveillance methods used in spontaneous reporting database.

The sensitivity of PRR and ROR in this study (49%) is higher than that found in two previous studies that showed sensitivity ranged from 9.9% to 28% [8,38]. One reason for this may be the different gold standard medicine-adverse event pairs used in our study. Our study used only statistically significant adverse events from powered randomised controlled trials as gold standard positive events, while the previous studies used all adverse events listed in the product information. Adverse events listed in the product information may be based on case reports and causality not substantiated. The specificity for PRR and ROR in prior studies was similar to the specificity in our study [6,8,38]. The predictive values for the BCPNN in our study (PPV: 51%, NPV: 81%) were similar with a previous study that used Martindale and Physician Desk Reference as the gold standard reference to evaluate safety signal using spontaneous reporting database (PPV: 44%, NPV: 85%) (7)].

Our findings suggest in cases where an adverse event has a prescription treatment or hospital admission that could describe the event, symmetry analysis may be employed in the administrative claims data as a complementary tool to spontaneous reporting of adverse event system. As with PRR, ROR and BCPNN methods, signals detected by SSA should not replace expert clinical review. SSA uses only prescription dispensing records and hospitalisation admission data without consideration of a patient's clinical condition. Positive signals generated for a medicine do not provide causal evidence that the medicine induced the event. Any positive signals generated by SSA should be followed up with a thorough investigation.

The strength of this study was that we used only adverse events identified in powered randomised controlled trials (RCTs) as the gold standard for positive events. In the real world, the types of adverse events reported to spontaneous reporting database may be different from those identified in the RCTs. The adverse events identified in RCTs are generally common and expected due to the mechanism of action of the medicine, thus these adverse events maybe unlikely to be reported to the spontaneous reporting centres. In addition, the FDA has a requirement that serious adverse events are to be reported to the

FDA reporting website [39]. However, in this study we found about 50% of the adverse events identified in RCTs such as nausea and diarrhoea could be detected from the FDA spontaneous reporting database. Other studies have also found that non-serious adverse events are commonly reported to spontaneous reporting databases [40-42]. Similarly, in administrative claims data, medicines used to treat adverse events may not always be recorded. Patients could either discontinue the suspected medicine that caused the event or switch to another medicine without having to be treated or hospitalised. Medicines used to treat adverse events are sometimes available as over-the-counter (OTC) medicines in pharmacy without having a prescription, meaning that the supply is not be recorded in the administrative claims data. The omission of OTC medicines could result in an underestimation of the sensitivity of sequence symmetry method. In essence, both types of databases used in this study have limitations as a source of data to detect common adverse events. However, this study has demonstrated that SSA that uses health claims data, together with PRR, ROR and BCPNN that use spontaneous reporting data can enhance ADR signal detection.

Conclusions

This study has demonstrated that sequence symmetry analysis that uses prescription and hospitalisation claims data may be a complementary pharmaco-surveillance tool to enhance the current quantitative methods that use spontaneous reporting data in detecting safety signals of medicines.

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