A Simulation-based Comparison of Drug-Drug Interaction Signal Detection Methods

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A Simulation-based Comparison of Drug-Drug Interaction Signal Detection Methods

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Contents

List of Tables.....iii

Abstract.....iv

1. Introduction.....1

2. A review of drug-drug interaction signal detection methods.....3

2.1 Notation.....3

2.2 Ω shrinkage method.....3

2.3 Chi-square statistics method.....4

2.4 Proportional reporting ratio (PRR).....5

2.5 Concomitant signal score (CSS).....6

2.6 Additive model.....6

2.7 Multiplicative model.....7

3. Simulation study.....8

4. Results.....9

4.1 Additive assumption.....9

4.2 Multiplicative assumption.....13

5. Application 16

6. Conclusion and Discussion 20

Reference 22

국문요약 25

List of Tables

Table 1..... 3

Table 2..... 11

Table 3..... 12

Table 4..... 14

Table 5..... 15

Table 6..... 19

Table 7..... 19

Abstract

Many studies have proposed methods to detect adverse drug reactions induced by taking two drugs together. These suspected adverse drug reactions can be discovered through post-market drug safety surveillance. Post-market drug safety surveillance relies on spontaneous reporting data including ADR reports and prescription information. Most previous studies have applied statistical models to real world data and compared the performance. In this article, we assess the performance of various detection methods by implementing simulations under various conditions. This allows us to determine which situation each of the methods is most useful for. In addition, we summarize and generalize the characteristics of each method.

Keywords: Drug-drug interaction, Adverse events, Post-market drug safety surveillance

1. Introduction

Polypharmacy, the use of multiple medicines has increased as the average life expectancy and the prevalence of multimorbidity has increased. Adverse events (AEs) caused by the administration of many drugs at the same time are therefore a serious concern. These suspected adverse drug reactions (ADRs) due to drug-drug interaction (DDI) can be discovered through post-market drug safety surveillance (PMS). Spontaneous reporting systems (SRSs) are databases used for PMS that include ADR reports and prescription information (e.g, sex, age, date, quantity, etc). By investigating SRS databases using data mining tools, we can identify signals and prevent the potential ADRs induced by DDI. Generally, quantitative DDI signals refer to excessive risk for a combination of two drugs compared with the risks for the individual drugs. However, the criteria used in each method to define signals are different and have various pros and cons.

Many previous studies have proposed approaches to detect signals indicating drug-drug interactions as well as single-drug adverse reactions. Norén et al. (2008) proposed the *Ω shrinkage measure* to screen for disproportional reporting indicative of suspected drug-drug interaction. Gosho et al. (2017) proposed the chi-square statistic as a statistical criterion for detecting drug-drug interaction signals and compared this method with Norén's using a simulation study. The proportional reporting ratio (PRR) proposed by Evan et al. (2001) was used to detect signals indicating single-drug reactions, then was extended for drug-drug interactions by Wang, X. et al. (2020). The

concomitant signal score (CSS), proposed by Noguchi et al. (2020), is an improved detection method using the PRR. Thakrar et al. (2007) proposed the additive and multiplicative model.

Many previous studies applied the statistical models to real world data, then compared the performance. A few studies have used simulation to evaluate the performance of various detection methods. The main purpose of this study is to assess the performance of various detection methods and to determine which situation each of methods is most useful for. In addition, by comparing the results, we can summarize and generalize the characteristics of each method.

Thus, in section 2, we provide an overview of existing methods. In section 3, we implement simulations in order to evaluate each method in terms of sensitivity and false positive rate. In section 4, we compare the performance of the signal detection algorithms for DDI in terms of sensitivity, false positive rate. In section 5, we applied DDI signal detection methods to the Korea Adverse Event Reporting System (KEARS) data (2017 – 2019) from the Korea Institute of Drug Safety and Risk Management (KIDS).

2. A review of drug-drug interaction signal detection methods

2.1 Notation

The methods are fundamentally based on the observed frequencies table presented in Table 1. Table 1 shows reported frequencies according to exposure status and adverse event (AE) status. Let f_{00} denote the relative reporting rate in the absence of both Drug 1 and Drug 2. Similarly, f_{10}, f_{01}, and f_{11} are, respectively, the relative reporting rate (i) with Drug 1 but not Drug 2, (ii) with Drug 2 but not Drug 1, and (iii) with concomitant use of the two drugs.

Table 1. Observed frequencies table for drug-drug-AE combinations

Exposure status		AE status		Relative reporting rate
Drug1	Drug2	Yes	No	
No	No	a	b	$f_{00} = a/(a+b)$
Yes	No	c	d	$f_{10} = c/(c+d)$
No	Yes	e	f	$f_{01} = e/(e+f)$
Yes	Yes	g	h	$f_{11} = g/(g+h)$

2.2 Ω shrinkage method

Norén et al. proposed the Ω shrinkage method. The Ω shrinkage method compares

the observed reporting rate f_{11} with its expected value $E[f_{11}]$ estimated under the assumption that there is no interaction between the two drugs. The estimator g_{11} of $E[f_{11}]$ is defined as:

$$g_{11} = 1 - \frac{1}{\max\left(\frac{f_{00}}{1-f_{00}}, \frac{f_{10}}{1-f_{10}}\right) + \max\left(\frac{f_{00}}{1-f_{00}}, \frac{f_{01}}{1-f_{01}}\right) - \frac{f_{00}}{1-f_{00}} + 1} \quad \textbf{(1)}$$

We define N=g as the observed report frequency, and E=$g_{11} \cdot (g + h)$ as the expected report frequency. The Ω shrinkage measure is defined as:

$$\Omega = log_2 \frac{N + \alpha}{E + \alpha} \quad \textbf{(2)}$$

where α represents the tuning parameters determining shrinkage strength. Generally, α is set to 0.5. The lower limit of the 95% confidence interval for Ω can be estimated as follows:

$$\Omega_{025} = \Omega - \frac{\phi(0.975)}{\log(2)\sqrt{N}} \quad \textbf{(3)}$$

where $\phi(0.975)$ is the 97.5th percentile of the standard normal distribution. The criterion $\Omega_{025} > 0$ is used to determine the drug-drug interaction (DDI) signal.

2.3 Chi-square statistics method

Gosho et al. (2017) proposed the chi-square statistic model in order to reduce the false positive rate when events are rare. The measure of the chi-square statistic method X is the

square root of the chi-square test statistic with a correction term.

$$\mathrm{X} = \frac{N - E - 0.5}{\sqrt{E}} \quad \textbf{(4)}$$

The threshold $X > 2$ and $X > 2.6$ is set for identifying DDI signals. These cutoff values are set based on the 95th and 99th percentiles, respectively, of the chi-square distribution with one degree of freedom.

2.4 Proportional reporting ratio (PRR)

The proportional reporting ratio is commonly used in disproportionality analysis to detect adverse event induced by a single drug. PRR is the ratio of observed reporting rate with or without a drug. PRR is extended to drug-drug interactions. First, PRR_{D1} for Drug1 and PRR_{D2} for Drug2 are defined as:

$$PRR_{D1} = \frac{(c+g)/(c+d+g+h)}{(a+e)/(a+b+e+f)} \quad \textbf{(5)}$$

$$PRR_{D2} = \frac{(e+g)/(e+f+g+h)}{(a+c)/(a+b+c+d)} \quad \textbf{(6)}$$

The PRR_{D1D2} for concomitant use of Drug1 and Drug2 is defined as:

$$PRR_{D1D2} = \frac{g/(g+h)}{(a+c+e)/(a+b+c+e+f)} \quad \textbf{(7)}$$

The lower limit of the 95% confidence interval for PRR is defined as:

$$PRR_{025} = e^{\ln PRR - 1.96SD} \quad \textbf{(8)}$$

Where the SD for Drug1 is $SD_{D1} = \sqrt{\frac{1}{c+g} - \frac{1}{c+d+g+h} + \frac{1}{a+e} - \frac{1}{a+b+e+f}}$, the SD for Drug2

is $SD_{D2} = \sqrt{\frac{1}{e+g} - \frac{1}{e+f+g+h} + \frac{1}{a+c} - \frac{1}{a+b+c+d}}$, and the SD for the Drug1-Drug2 pair is $SD_{D1D2} = \sqrt{\frac{1}{g} - \frac{1}{g+h} + \frac{1}{a+c+e} - \frac{1}{a+b+c+d+e+f}}$. The signal detection criterion is to compare the lower limit of the 95% confidence interval for a single drug and drug-drug pairs. If $PRR_{025D1D2} > \max(PRR_{025D1}, PRR_{025D2})$, then the drug pair is considered to be a signal of DDI.

2.5 Concomitant signal score (CSS)

The concomitant signal score, proposed by Noguchi et al. (2021), was shown to improve the combination risk ratio (CRR), a DDI detection method using PRR. The weakness of CRR is that the lower limit of the 95% CI of PRR_{D1D2} overlaps with the upper limit of the 95% CI of PRR_{D1}or PRR_{D2}. This is because adverse event reports involving individual drugs are more common than reports concerning the concomitant use of two drugs. The concomitant signal score is the ratio of $PRR_{025D1D2}$ and the maximum value between PRR_{975D1} and PRR_{975D2}.

$$Concomitant\ signal\ score\ (CSS) = \frac{PRR_{025D1D2}}{\max\ (PRR_{975D1}, PRR_{975D2})} \quad \textbf{(9)}$$

The signal detection criteria are (1) $PRR_{025D1D2} > 1$, (2) CSS > 1.

2.6 Additive model

Thakrar et al. proposed the additive model for the detection of DDI signals. The

additive model assumes that the risk associated with a drug adds to the background risk. Under the additive assumption, no interaction is established when the excess risk associated with the drug combination is the same as the sum of the excess risks associated with each exposure in the absence of the other. The risk difference is defined as $RD_{AB} = f_{11} - f_{00}$, $RD_A = f_{10} - f_{00}$, and $RD_B = f_{01} - f_{00}$. When $RD_{AB} > RD_A + RD_B$, the signal is detected. That is, f_{11}-f_{10}-f_{01}+f_{00} statistically significantly greater than 0 indicate a positive interaction. Therefore, we fit the linear probability model and test the interaction term.

$$risk\ of\ event = \alpha + \beta_1 Drug1 + \beta_2 Drug2 + \beta_3 Drug1 * Drug2 \quad \textbf{(10)}$$

When β_3 is statistically significantly greater than 0, there is a potential DDI.

2.7 Multiplicative model

Thakrar et al. proposed the multiplicative model for the detection of DDI signals. The multiplicative model assumes that the risk associated with a drug multiplies with the background risk. The risk ratio is defined as $RR_{AB} = \frac{f_{11}}{f_{00}}$, $RR_A = \frac{f_{10}}{f_{00}}$, and $RR_B = \frac{f_{01}}{f_{00}}$. When $RR_{AB} > RR_A \times RR_B$, the signal is detected. When $\frac{RR_{AB}}{RR_A \times RR_B}$ is statistically significantly greater than 1, there is a signal indicating a potential DDI. Likewise, we implement the log linear regression to test the interaction term.

$$log\ (risk\ of\ event) = \alpha + \beta_1 Drug1 + \beta_2 Drug2 + \beta_3 Drug1 * Drug2 \quad \textbf{(11)}$$

When β_3 is statistically significantly greater than 0, there is a potential DDI.

3. Simulation study

We generated data from a binomial distribution in each row of Table 1. The incidence probability of an adverse event f was set differently for each scenario. The data generation was repeated 3,000 times in each setting. We implemented simulations under the additive assumption and multiplicative assumption.

In scenario 1, we assumed that there is no interaction under the additive assumption to evaluate the false positive rate. (1-1) assumed that there is no effect of each single drug and no interaction; (1-2) assumed that there is an effect of Drug2, but no interaction; (1-3) assumed that there is an effect of Drug1 and Drug2, but no interaction; and (1-4) assumed that the effect of Drug2 is greater than that of Drug1.

In scenario 2, we assumed that there is a positive interaction to evaluate sensitivity. (2-1) assumed that there is an interaction but no effect of each single drug; (2-2) assumed that there is an effect of Drug2, and interaction; (2-3) assumed that there is an effect of Drug1 and Drug2, and an interaction; and (2-4) assumed that the effect of Drug2 is greater than that of Drug1.

In scenario 3, we assumed that there is no interaction under the multiplicative assumption to evaluate the false positive rate. Following the structure of scenario 1, scenarios (3-1), (3-2), (3-3), and (3-4) were implemented.

In scenario 4, we assumed that there is a positive interaction under the multiplicative

assumption to evaluate sensitivity. Following the structure of scenario 2, scenarios (4-1), (4-2), (4-3), and (4-4) were implemented.

4. Results

4.1 Additive assumption

The false positive rate of the Ω method ranged from 0.001 to 0.055. The false positive rate of the chi-square method with threshold=2 was similar to that of the Ω method: between 0.001 and 0.066. The false positive rate of the chi-square method with threshold=2.6 showed the smallest variation, ranging from 0.000 to 0.029, while the PRR method showed a wide range of false positive rate, ranging from 0.006 to 0.127.

The Ω method and the chi-square method with threshold=2 controlled the false positive rate below 0.05 and had high sensitivity in most scenarios. In particular, when the number of events is small ($g < 2$), the chi-square method has a higher sensitivity than the Ω method. The CSS method showed the lower false positive rate than the Ω method or the chi-square method, but it also showed the lower sensitivity. This may be due to the lower threshold for the measure of the CSS method to reach an interaction. Comparing the additive and the multiplicative model, when there is no effect of each single drug or there is an effect of Drug2 only (scenarios (2-1) and (2-2)), the multiplicative model showed the higher sensitivity than the additive model. On the other hand, when there is an effect of

Drug1 and Drug2 (scenarios (2-3) and (2-4)), the additive model showed the higher sensitivity than the multiplicative model. Scenarios (2-3) and (2-4) are more realistic conditions. Indeed, when we applied both models to real world data, the additive model detected a signal of DDI that the multiplicative model couldn't detect.

Comparing scenarios (2-3) and (2-4), most methods except the multiplicative model showed the higher sensitivity in the scenario (2-4). That is, when the difference between the effects of the two drugs is large, the sensitivity increases.

Table 2. False-positive rate in simulation scenario 1

Incidence probability for AE(%)						False positive rate						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 1-1												
0.005	0.005	0.005	0.005	1.5	1.4	0.008	0.013	0.005	0.012	0.003	0.001	0.065
0.05	0.05	0.05	0.05	6.0	7.2	0.007	0.006	0.002	0.017	0.005	0.020	0.055
0.5	0.5	0.5	0.5	50.9	55.3	0.001	0.001	0.000	0.010	0.004	0.029	0.037
Scenario 1-2												
0.001	0.001	0.005	0.005	1.5	0.9	0.031	0.049	0.025	0.013	0.002	0.001	0.003
0.01	0.01	0.05	0.05	6.0	6.5	0.032	0.028	0.008	0.013	0.008	0.016	0.027
0.1	0.1	0.5	0.5	51.0	53.4	0.003	0.003	0.000	0.006	0.002	0.031	0.026
Scenario 1-3												
0.001	0.003	0.003	0.005	1.5	0.8	0.039	0.066	0.029	0.083	0.004	0.001	0.002
0.01	0.03	0.03	0.05	5.9	5.1	0.054	0.048	0.015	0.127	0.051	0.011	0.000
0.02	0.05	0.05	0.08	8.9	8.1	0.055	0.049	0.017	0.114	0.074	0.019	0.000
Scenario 1-4												
0.002	0.003	0.006	0.007	1.7	1.1	0.045	0.058	0.029	0.029	0.005	0.001	0.008
0.002	0.003	0.015	0.016	2.6	2.0	0.046	0.053	0.023	0.023	0.005	0.006	0.002
0.002	0.003	0.03	0.031	4.1	3.6	0.050	0.045	0.017	0.006	0.001	0.009	0.000

Table 3. Sensitivity in simulation scenario 2

Incidence probability for AE(%)						Sensitivity						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 2-1												
0.001	0.001	0.001	0.005	1.5	0.5	0.090	0.205	0.112	0.185	0.013	0.005	0.042
0.01	0.01	0.01	0.05	6.0	2.1	0.581	0.584	0.436	0.567	0.506	0.493	0.764
0.1	0.1	0.1	0.5	51.0	13.2	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Scenario 2-2												
0.001	0.001	0.002	0.005	1.5	0.6	0.075	0.140	0.084	0.094	0.011	0.002	0.024
0.01	0.01	0.02	0.05	6.0	3.0	0.332	0.329	0.218	0.387	0.244	0.252	0.409
0.1	0.1	0.2	0.5	51.1	23.0	0.999	0.999	0.994	1.000	1.000	1.000	1.000
Scenario 2-3												
0.001	0.002	0.002	0.005	1.5	0.6	0.069	0.119	0.069	0.118	0.008	0.001	0.011
0.01	0.02	0.02	0.05	5.9	3.2	0.293	0.284	0.170	0.368	0.185	0.110	0.089
0.1	0.2	0.2	0.5	51.0	28.4	0.986	0.983	0.939	1.000	1.000	0.973	0.409
Scenario 2-4												
0.001	0.002	0.004	0.008	1.8	0.8	0.096	0.126	0.073	0.158	0.011	0.006	0.007
0.01	0.02	0.04	0.08	9.0	5.2	0.348	0.326	0.187	0.295	0.219	0.171	0.026
0.1	0.2	0.4	0.8	81.0	45.2	1.000	1.000	1.000	1.000	1.000	1.000	0.027

4.2 Multiplicative assumption

In this section, we implemented simulations by setting incidence f under the multiplicative assumption. The reason for simulations under the multiplicative assumption was to examine the false positive rate and sensitivity when the definition of interaction was changed. In scenario 3 comparing false positive rate, scenarios (3-1) and (3-2) are the same with scenarios (1-1) and (1-2) because they satisfy both the additive assumption and multiplicative assumption. In scenario 4 comparing sensitivity, scenarios (4-1), (4-2), and (4-3) are equivalent to scenarios (2-1), (2-2), and (2-3) because they also satisfy both the additive assumption and multiplicative assumption. It can be shown that satisfying the multiplicative assumption will imply satisfying the additive assumption, thus the additive model has the lower threshold for incidence f to reach an interaction,

The detection signals of the multiplicative model mean stronger interactions than those of the additive model. By comparison, the additive model can detect the DDI signal earlier. The multiplicative model can help determine whether there is stronger evidence of DDI after checking DDI with the additive model.

Table 4. False positive rate in simulation scenario 3

Incidence probability for AE(%)						False positive rate						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 3-1												
0.005	0.005	0.005	0.005	1.5	1.3	0.006	0.112	0.003	0.086	0.002	0.000	0.063
0.05	0.05	0.05	0.05	6.0	7.3	0.006	0.004	0.000	0.002	0.004	0.013	0.052
0.5	0.5	0.5	0.5	51.0	54.8	0.000	0.001	0.000	0.000	0.005	0.028	0.033
Scenario 3-2												
0.001	0.001	0.005	0.005	1.5	0.9	0.038	0.061	0.028	0.017	0.003	0.002	0.002
0.01	0.01	0.05	0.05	5.9	6.4	0.024	0.020	0.007	0.014	0.004	0.013	0.028
0.1	0.1	0.5	0.5	51.0	53.0	0.003	0.002	0.000	0.004	0.002	0.035	0.026
Scenario 3-3												
0.001	0.002	0.002	0.004	1.4	0.6	0.049	0.091	0.047	0.062	0.004	0.001	0.006
0.0018	0.003	0.003	0.005	1.5	0.7	0.042	0.075	0.037	0.085	0.006	0.000	0.022
0.018	0.03	0.03	0.05	6.0	4.4	0.113	0.106	0.049	0.119	0.058	0.034	0.047
Scenario 3-4												
0.001875	0.003	0.005	0.008	1.8	0.9	0.069	0.107	0.049	0.137	0.015	0.002	0.018
0.01875	0.03	0.05	0.08	9.0	6.3	0.188	0.170	0.084	0.180	0.117	0.085	0.038
0.04375	0.05	0.07	0.08	9.0	8.3	0.054	0.048	0.015	0.039	0.019	0.026	0.046

Table 5. Sensitivity in simulation scenario 4

Incidence probability for AE(%)						Sensitivity						
						Ω shrinkage method	X^2 statistics method		PRR	CSS	Additive	Multiplicative
f_{00}	f_{10}	f_{01}	f_{11}	g	E		$X_{threshold=2}$	$X_{threshold=2.6}$				
Scenario 4-1												
0.001	0.001	0.001	0.005	1.5	0.5	0.080	0.213	0.126	0.261	0.013	0.004	0.040
0.01	0.01	0.01	0.05	6.0	2.2	0.538	0.541	0.393	0.565	0.496	0.494	0.765
0.1	0.1	0.1	0.5	50.9	13.0	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Scenario 4-2												
0.001	0.001	0.002	0.005	1.5	0.5	0.079	0.160	0.091	0.113	0.011	0.003	0.019
0.01	0.01	0.02	0.05	5.9	3.0	0.369	0.319	0.212	0.380	0.236	0.250	0.410
0.1	0.1	0.2	0.5	50.9	22.7	1.000	1.000	0.998	1.000	1.000	1.000	1.000
Scenario 4-3												
0.001	0.002	0.002	0.005	1.5	0.6	0.067	0.112	0.061	0.085	0.007	0.001	0.009
0.01	0.02	0.02	0.05	6.0	3.2	0.309	0.296	0.176	0.393	0.198	0.112	0.085
0.1	0.2	0.2	0.5	51.1	28.4	0.988	0.985	0.937	1.000	1.000	0.969	0.398
Scenario 4-4												
0.0008	0.001	0.003	0.005	1.5	0.5	0.084	0.153	0.096	0.100	0.007	0.002	0.003
0.008	0.01	0.03	0.05	6.0	3.8	0.207	0.190	0.103	0.134	0.074	0.092	0.087
0.08	0.1	0.3	0.5	51.0	31.7	0.937	0.922	0.774	0.913	0.891	0.938	0.496

5. Application

We applied DDI signal detection methods to Korea Adverse Event Reporting System (KEARS) data from the Korea Institute of Drug Safety and Risk Management (KIDS) in 2017-2019. Known interaction was derived from a research report published by the Health Insurance Review and Assessment Service (HIRA) on the adverse event monitoring system, and the list of contraindications of co-medication drugs was derived from KIDS (as of Dec. 28, 2020). In addition, suspected interaction pairs were selected from the combination of drug-drug-AE that has high frequency in KEARS data.

A total of 1,131,985 reports were taken from the KEARS. Among them, there were 1656 cases of hyperkalemia and284 cases of QT prolongation. Hyperkalemia is defined as an elevation in serum potassium to a value greater than 5 mmol/L (Evans et al., 2005). Potassium chloride is prescribed for potassium-deficiency, electrolyte imbalance, and digitalis poisoning. Spironolactone is a diuretic. Tactolimus is an intensive immunosuppressant agent used to prevent transplant rejection. According to the HIRA research report, co-administration of potassium chloride and spironolactone was reported to cause hyperkalemia. QT prolongation was defined as a QT interval greater than 450 ms in woman and greater than 440 ms in man. Prolongation of the QT interval is associated with an increased risk of development of a potentially lethal cardiac arrhythmia called *torsade de pointes*, a risk that increases with the administration of a QT-prolonging drugs (Beny Charbit et al., 2006). Domperidone is a drug that increases gastrointestinal motility

and is prescribed for indigestion and vomiting. Amiodarone is an antiarrhythmic drug.

The relative reporting rate for the exposure status of each drug-drug pair was summarized in Table 6. The measure of six methods for the six drug-drug-AE combinations was summarized in Table 7. In Table 7, “domperidone - amiodarone / QT prolongation” which is known interaction, was detected as a potential signal by the Ω method, the chi-square method, the PRR method, the CSS method, and the additive model. “Domperidone - amiodarone” had the small number of reports for the combination (about 18), but its reporting proportions were 222.2 per 1000 for domperidone-amiodarone combination. It was much larger than the reporting proportion of the other two pairs (53.6 per 1000 for potassium chloride - spironolactone, 62.5 per 1000 for tacrolimus - spironolactone). The multiplicative showed a positive interaction trend for domperidone - amiodarone combination, but it did not show the statistical significance (p-value=0.185).

“Acetylsalicylic acid - polystyrene sulfonate / hyperkalemia” which is a suspected interaction, was detected as a potential signal by the Ω method, the chi-square method, and the PRR method. The reporting proportion of “acetylsalicylic acid - polystyrene sulfonate” was 47.9 per 1000, the largest of the three suspected interactions. While the combination of acetylsalicylic acid and polystyrene sulfonate was not previously known interaction, DDI signals were detected among the suspected combinations that has a large number of AE reports. However, it is difficult to accept strong evidence of DDI since only three of the six methods identified DDI.

For known interactions, only one drug-drug pair (domperidone- amiodarone) was detected and the other two combinations were not exactly identified. The reason for the reduced sensitivity may be that the number of cases is very small because it is rare to prescribe combinations that are known to have side effects when taken together.

Table 6. The proportion of adverse event in the exposure status of each drug-drug pair

Drug-drug pair	Adverse event	No A, No B	A, No B	No A, B	A and B
Known interaction					
Potassium chloride(A)-spironolactone(B)	Hyperkalemia	1132/1145114	7/2308	505/4813	12/224
Tacrolimus(A)-spironolactone(B)	Hyperkalemia	1023/1143317	116/4105	515/5005	2/32
Domperidone(A)-amiodarone(B)	QT prolongation	252/1147706	3/2728	25/1533	4/18
Suspected interaction					
Carvedilol(A)-spironolactone(B)	Hyperkalemia	1103/1140660	36/6762	497/4107	20/930
Acetylsalicylic acid(A)- polystyrene sulfonate(B)	Hyperkalemia	1541/1124513	43/25783	50/1704	22/459
Acetylsalicylic acid(A)-amiodarone(B)	QT prolongation	254/1124458	1/25976	25/1285	4/266

Table 7. The measure of each method applied to drug-drug / adverse events

Drug-drug / adverse event	Ω	X^2	PRR		CSS	Additive		Multiplicative	
			$PRR_{025D1D2}$	max		β_3	p-value	β_3	p-value
Known interaction									
Potassium chloride-spironolactone / Hyperkalemia	-1.780	-2.532	21.607	93.542	0.190	-0.053	0.001	-1.793	0.000
Tacrolimus-spironolactone / Hyperkalemia	-2.848	-1.250	11.371	93.542	0.010	-0.678	0.116	-3.951	0.000
Domperidone-amiodarone / QT prolongation	1.062	5.741	382.197	57.637	3.096	0.205	0.037	1.001	0.185
Suspected interaction									
Carvedilol-spironolactone / Hyperkalemia	-3.135	-8.942	9.786	93.542	0.086	-0.104	0.000	-3.433	0.000
Acetylsalicylic acid- polystyrene sulfonate/ Hyperkalemia	0.072	2.143	22.412	19.160	0.735	0.018	0.090	0.294	0.317
Acetylsalicylic acid-amiodarone / QT prolongation	-1.749	-0.736	23.223	57.637	0.188	-0.004	0.614	1.511	0.183

6. Conclusion and discussion

As the number of patients with chronic disease becomes more common, the co-prescription of multiple drugs has increased. Therefore, it has become more important to identify combinations of drugs that have side effects through post-market drug safety surveillance. In this article, we examined statistical methodologies for DDI signal detection. Of the six methods, the Ω shrinkage method and the chi-square method show the best performance. The Ω shrinkage method and the chi-square method with threshold=2 controlled the false positive rate below 0.05 and had high sensitivity in most scenarios. The chi-square method is especially effective when AE has a small number of reports ($g<2$). The chi-square method with threshold=2.6 and the additive model are conservative methods. They rigorously control the FPR, but they had lower sensitivity than the Ω shrinkage method and the chi-square method with threshold=2.

An important consideration is that spontaneous reporting system databases may result in bias due to underreporting. Since underreporting information is not included in the collected data, it cannot be considered. Thus, it is likely to have a significant impact on DDI signal detection. Furthermore, the six methods introduced in this paper identify DDI using an interaction signal indicator defined by an equation. Therefore, there is a limitation in that the definition of a true DDI signal depends on the measure of each methods.

The aforementioned methods have the advantage of being easy to apply and easy to calculate, but the sole use of individual method is not adequate. It is recommended to use the other methods at the same time. Also, pharmacological mechanisms for drug-drug

interactions should be considered. The DDI signal detection considering clinical aspects may further improve the limitations of statistical DDI signal detection methods.

References

Evans, S. J., Waller, P. C., & Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, *10*(6), 483 – 486.

Gosho, M., Maruo, K., Tada, K., & Hirakawa, A. (2017). Utilization of chi-square statistics for screening adverse drug-drug interactions in spontaneous reporting systems. *European journal of Clinical Pharmacology*, *73*(6), 779 – 786.

Heba, I., Amany, A., Ahmed, S. E., & Amr, S. (2014). Novel data-mining methodologies for detecting drug-drug interactions: a review of pharmacovigilance literature. *Advances in Environmental Sciences, Development and Chemistry*, *20*, 301 – 14.

Masnoon, N., Shakib, S., Kalisch-Ellett, L., & Caughey, G. E. (2017). What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*, *17*(1), 1 – 10.

Noguchi, Y., Ueno, A., Otsubo, M., Katsuno, H., Sugita, I., Kanematsu, Y., ... & Teramachi, H. (2018). A new search method using association rule mining for drug-drug interaction based on spontaneous report system. *Frontiers in pharmacology*, *9*, 197.

Noguchi, Y., Tachi, T., & Teramachi, H. (2019). Review of statistical methodologies for detecting drug–drug interactions using spontaneous reporting systems. *Frontiers in Pharmacology*, *10*, 1319.

Noguchi, Y., Tachi, T., & Teramachi, H. (2020). Comparison of signal detection algorithms based on frequency statistical model for drug-drug interaction using spontaneous reporting systems. *Pharmaceutical Research*, *37*(5), 1 – 10.

Norén, G. N., Sundberg, R., Bate, A., & Edwards, I. R. (2008). A statistical methodology for drug–drug interaction surveillance. *Statistics in Medicine*, *27*(16), 3057 – 3070.

Qian, Y., Ye, X., Du, W., Ren, J., Sun, Y., Wang, H., ... & He, J. (2010). A computerized system for detecting signals due to drug–drug interactions in spontaneous reporting systems. *British journal of clinical pharmacology*, *69*(1), 67 – 73.

Tatonetti, N. P., Fernald, G. H., & Altman, R. B. (2012). A novel signal detection algorithm for identifying hidden drug-drug interactions in adverse event reports. *Journal of the American Medical Informatics Association*, *19*(1), 79-85.

Thakrar, B. T., Grundschober, S. B., & Doessegger, L. (2007). Detecting signals of drug–drug interactions in a spontaneous reports database. *British Journal of Clinical Pharmacology*, *64*(4), 489 – 495.

Wang, X., Li, L., Wang, L., Feng, W., & Zhang, P. (2020). Propensity score-adjusted three-component mixture model for drug-drug interaction data mining in FDA Adverse Event Reporting System. *Statistics in Medicine*, *39*(7), 996 – 1010.

World Health Organization. (2004). *A glossary of terms for community health care and services for older persons*. WHO.

Zhang, P., Li, M., Chiang, C. W., Wang, L., Xiang, Y., Cheng, L., ... & Li, L. (2018). Three-component mixture model-based adverse drug event signal detection for the adverse event reporting system. *CPT: pharmacometrics & systems pharmacology*, *7*(8), 499-506.

김동숙, 변지혜, 조도연, 신혜림, 김병수, 김묘정, ... & 이용석. (2019). 약물부작용 후향적 분석 및 부작용 모니터링 시스템 기반 마련.

국 문 요 약

많은 선행연구에서 두 가지 약물을 함께 복용함으로 인해 발생하는 약물 부작용을 탐지하는 방법을 연구하였다. 약물 부작용으로 의심되는 신호는 시판 후 의약품 안전 감시를 통하여 발견될 수 있다. 시판 후 의약품 안전 감시는 부작용 보고와 의약품 처방 정보에 대한 자발적 보고 데이터에 기반한다. 약물간 상호작용 신호 탐지방법에 대한 대부분의 선행 연구는 이러한 자발적 보고 데이터에 각 방법들을 적용하고 각 방법들 간의 성능을 비교하였다. 본 논문에서는 다양한 조건하에서 시뮬레이션을 수행하여 여러 방법들 간의 성능을 평가한다. 이를 통해 각 방법의 특성을 요약하고 어떤 상황에서 유용한지 살펴보고자 한다.

핵심되는 말 : 약물간 상호작용, 의약품 부작용, 시판 후 의약품 안전감시