Prescription sequence symmetry analysis: assessing risk, temporality, and consistency for adverse drug reactions across datasets in five countries

Nicole Pratt¹, Esther W. Chan², Nam-Kyong Choi³, Michio Kimura⁴, Tomomi Kimura⁴, Kiyoshi Kubota⁵, Edward Chia-Cheng Lai⁶, Kenneth K. C. Man², Nobuhiro Ooba⁵, Byung-Joo Park⁷,⁸, Tsugumichi Sato⁷, Ju-Young Shin⁸, Ian C. K. Wong², Yea-Huei Kao Yang⁶ and Elizabeth E. Roughead¹*

¹Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia
²Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Pok Fu Lam, Hong Kong
³Medical Research Collaborating Centre, Seoul National University College of Medicine/Seoul National University Hospital, Seoul, South Korea
⁴Department of Medical Informatics, Hamamatsu University School of Medicine, Shizuoka, Japan
⁵Department of Pharmacoepidemiology, University of Tokyo Graduate School of Medicine, Tokyo, Japan
⁶Institute of Clinical Pharmacy and Pharmaceutical Sciences, Health Outcome Research Centre, National Cheng Kung University, Tainan City, Taiwan
⁷Department of Preventative Medicine, Seoul National University College of Medicine, Seoul, South Korea
⁸Korea Institute of Drug Safety and Risk Management, Seoul, South Korea

ABSTRACT

Background Prescription sequence symmetry analysis (PSSA) is a signal detection method for adverse drug events. Its capacity to consistently detect adverse drug events across different settings has not been tested. We aimed to determine the consistency of PSSA results for detecting positive and negative control adverse drug events across different settings.

Methods Using a distributed network model, we analyzed prescription dispensing data using PSSA in Australia, Hong Kong, Japan, Korea, and Taiwan. Positive control was amiodarone and thyroxine, as a marker of amiodarone-induced hypothyroidism, a known adverse event with a clear temporal relationship to amiodarone initiation. Negative controls were amiodarone and allopurinol, as a marker of amiodarone-induced gout and thyroxine and allopurinol, as a marker of thyroxine-induced gout. Gout is not recorded as an adverse event in product information for either medicine. Adjusted sequence ratios (ASR) were calculated for each country. Pooled estimates were obtained by using the generic inverse variance method.

Results A positive association was identified between amiodarone and thyroxine in all settings with a pooled ASR 2.63 (95% confidence interval (CI) 1.47–4.72). Temporal analysis showed the effect occurred within the first few weeks of treatment. No significant associations were found for the negative controls in any setting; pooled ASR were 0.76 (95%CI 0.62–0.93) and 0.98 (95%CI 0.85–1.12) for amiodarone-allopurinol and thyroxine-allopurinol, respectively.

Conclusion Despite different health settings, different populations, and different patterns of medicine utilization, PSSA gave consistent estimates across countries for a well-known positive association and two negative control adverse events. © 2015 The Authors Pharmacoepidemiology and Drug Safety Published by John Wiley & Sons Ltd.

KEY WORDS—prescription symmetry analysis; pharmacovigilance; amiodarone; hyperthyroidism; pharmacoepidemiology

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BACKGROUND

Prescription sequence symmetry analysis (PSSA) is a signal detection method for adverse drug events utilizing administrative claims data.¹ The method has the
potential to become a tool to assist in global pharmacoepidemiology of medicines, complementary to other methods, because of its ease of application. The method employs a simple algorithm, is computationally fast, and requires a minimal dataset of only three variables: drug name, date of supply, and a patient identifier. This minimal dataset is usually captured in electronically held prescription dispensing datasets, which are available in many developed countries, thus enabling multi-country analyses.

We have previously shown that PSSA has a sensitivity of 61%, a specificity of 93%, a positive predictive value of 77%, and a negative predictive value of 87% using adverse events identified in randomized controlled trials as the gold standard for positive events and using negative controls of adverse events identified in product information of unrelated products.2 We have also shown the feasibility of the method in a distributed network model to undertake multi-country analyses.3

The Bradford Hill criteria for causal association identify temporality and consistency as important criteria for assessing causation of events.4 One of the advantages of PSSA over other methods is that a visualization of temporal association is created in addition to the statistical output of an adjusted sequence ratio. By applying the method across multiple datasets, we also have the opportunity to test consistency across time. Thus, PSSA is a potentially valuable method for assessing both temporality and consistency. In our prior study, where we assessed the association between antipsychotics and acute hyperglycaemia,3 we found that the adjusted analyses for individual medicines were similar in the direction of the associations across countries; however, some countries had outlying results. Differences between countries in terms of stigma associated with mental health treatment were postulated as one of the reasons for the discrepancy. For this reason, the present validation study aimed to identify whether a well-known medicine adverse event that was unlikely to be confounded by health system factors could be consistently detected across countries.

In this study, we aimed to assess whether PSSA provides temporally associated and consistent results across multiple datasets in different countries.

This research was undertaken utilizing the network of databases established as part of the Asian Pharmacoepidemiology network (AsPEN).5 AsPEN enables studies to be undertaken in datasets within different countries, with different ethnic groupings and different health systems and regulations.

METHOD

In selecting the positive control, we identified a medicine that was available in every country and had a well-documented adverse event for which there was a specific prescription treatment and for which there was evidence of a temporal association. The positive control, or known adverse event, in this study was amiodarone-induced hypothyroidism. Amiodarone is an antiarrhythmic agent that contains iodine in its chemical structure and is known to exert effect on the thyroid gland6 with an estimated incidence of thyroid dysfunction of 15–20% in persons taking amiodarone.7 Amiodarone-induced hypothyroidism has been reported to occur early in the course of therapy and has an incidence of approximately 5–7%;8–10 thus, we would expect to see a temporal association of the adverse event with initiation. A nested case–control study found the risk of hypothyroidism was increased more than sixfold (Odds ratio 6.6, 95% confidence interval (CI) 3.9–11.1) in those taking amiodarone.11 A meta-analysis of adverse events from randomized controlled trials comparing amiodarone with placebo that grouped adverse events by organ class found a fourfold increased risk (OR 4.2, 95% CI 2.0–8.7) of adverse thyroid events with amiodarone.12 For the negative controls, or known negative events, we assessed amiodarone-induced allopurinol prescribing and thyroxine-induced allopurinol prescribing. Allopurinol, which is indicated for prevention of gout but not acute treatment of gout, was chosen as the negative control because neither amiodarone nor thyroxine is known to be associated with gout.13 Furthermore, given allopurinol is indicated for prevention, but not for treatment of an acute gout event, it is unlikely to be prescribed, even if a previously unrecognized adverse event occurred.

The AsPEN participants in this study were based in Australia, Hong Kong, Japan, Korea, and Taiwan. The datasets have been described previously.5 The Australian Government Department of Veterans’ Affairs healthcare claims database (Australia, 2001–2012) contains dispensing records for all veterans and their dependents in Australia (approximately 300 000) and represents a predominantly elderly cohort. The Korea Health Insurance Review and Assessment Service database (Korea, 2006–2008) includes all subsidized medicines for the entire population of approximately 50 million persons. The National Health Insurance Research Database (Taiwan, 2002–2008) includes all subsidized medicines covering the entire population; a random sample of one million persons was included in this...
The Hong Kong dataset was the Clinical Data Analysis and Reporting System from the Hong Kong Hospital Authority (2008–2012). The Hong Kong dataset includes data from publicly funded hospitals and primary care general physician services via the outpatient clinics in hospitals and general outpatient clinics in the community. The service is available to all Hong Kong residents. The dataset covers a population of approximately seven million. Data were also sourced from the Japan Medical Data Center insurance claims database (Japan, 2005–2010), which represents a privately insured population of approximately 300,000 adult working population and their dependents; however, there were insufficient records, and so data from this dataset were not included in the study. Data from a hospital-based database were also included, the Hamamatsu Medical University Database, Japan (1999–2010). The Japanese hospital dataset includes all patients attending the hospital (approximately 175,000) but does not include community records.

A distributive network model was employed.\(^3\) Participants created a dataset that included (i) a unique patient identifier; (ii) a variable to identify the medicine dispensed based on the World Health Organization standard anatomical therapeutic chemical (ATC) code; and (iii) a variable to identify the date of medicine supply. The coordinating center for this study. The Hong Kong dataset was the Clinical Data Analysis and Reporting System from the Hong Kong Hospital Authority (2008–2012). The Hong Kong dataset includes data from publicly funded hospitals and primary care general physician services via the outpatient clinics in hospitals and general outpatient clinics in the community. The service is available to all Hong Kong residents. The dataset covers a population of approximately seven million. Data were also sourced from the Japan Medical Data Center insurance claims database (Japan, 2005–2010), which represents a privately insured population of approximately 300,000 adult working population and their dependents; however, there were insufficient records, and so data from this dataset were not included in the study. Data from a hospital-based database were also included, the Hamamatsu Medical University Database, Japan (1999–2010). The Japanese hospital dataset includes all patients attending the hospital (approximately 175,000) but does not include community records.

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### Table 1. Prescription sequence symmetry analysis results for the association between amiodarone and thyroxine: positive control

<table>
<thead>
<tr>
<th>Country</th>
<th>N pairs</th>
<th>Amiodarone first</th>
<th>Thyroxine first</th>
<th>Adjusted sequence ratio, 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1979</td>
<td>1663</td>
<td>316</td>
<td>5.30 (4.69–5.96)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>754</td>
<td>529</td>
<td>225</td>
<td>2.33 (1.99–2.72)</td>
</tr>
<tr>
<td>Japan</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>1.77 (1.06–5.08)</td>
</tr>
<tr>
<td>Korea</td>
<td>657</td>
<td>453</td>
<td>204</td>
<td>1.52 (1.29–1.80)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>153</td>
<td>115</td>
<td>38</td>
<td>3.26 (2.26–4.70)</td>
</tr>
</tbody>
</table>

### Figure 1. Temporal analysis positive control: amiodarone-thyroxine, Australia

![Temporal analysis positive control: amiodarone-thyroxine, Australia](image)

### Figure 2. Pooled analysis positive control: amiodarone-thyroxine. CI, confidence interval; SE, standard error

![Pooled analysis positive control: amiodarone-thyroxine](image)
Table 2. Prescription sequence symmetry analysis results for the association between amiodarone and allopurinol: negative control

<table>
<thead>
<tr>
<th>Country</th>
<th>N pairs</th>
<th>Amiodarone first</th>
<th>Allopurinol first</th>
<th>Adjusted sequence ratio, 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1002</td>
<td>493</td>
<td>509</td>
<td>0.99 (0.88–1.12)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>434</td>
<td>179</td>
<td>255</td>
<td>0.70 (0.58–0.85)</td>
</tr>
<tr>
<td>Japan</td>
<td>23</td>
<td>9</td>
<td>14</td>
<td>0.65 (0.28–1.49)</td>
</tr>
<tr>
<td>Korea</td>
<td>812</td>
<td>266</td>
<td>546</td>
<td>0.67 (0.57–0.77)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>384</td>
<td>148</td>
<td>236</td>
<td>0.72 (0.59–0.88)</td>
</tr>
</tbody>
</table>

Figure 3. Temporal analysis negative control: amiodarone-allopurinol, Australia

Figure 4. Pooled analysis negative control: amiodarone-allopurinol. CI, confidence interval; SE, standard error

study, the University of South Australia, developed the statistical analysis code as a stand-alone Statistical Analysis System program for execution by each participant. The SAS program employed global macro variables that required participants to enter the variable names used in their datasets rather than forcing the creation of a data file with common data variable names. This approach eliminates a complex programming burden for participants and overcomes barriers because of language and disparate data structures. Participants executed the SAS code, and a standardized summary results file was returned to the coordinating center for collation. These standardized files included graphs of the number of people dispensed amiodarone, thyroxine, and allopurinol each month (prevalent population), the number of people starting amiodarone, thyroxine, and allopurinol each month (incident population), and the prescription symmetry analyses including the PSSA distribution graphs, which display the temporal relationship between dispensing. Medicines were selected by ATC codes in the Australian, Korean, and Taiwanese datasets: amiodarone C01BD01, allopurinol M04AA01, and thyroxine H03AA01. Codes for medicines in the Hong Kong and Japanese datasets were mapped to the ATC codes.
In the PSSA method, the date of incident dispensing of amiodarone, thyroxine, and allopurinol was determined for each individual patient. All incident dispensing that occurred within 1 year of each other for the same person were included in the analysis. We excluded patients who initiated any of the study medicines in the first year of data coverage in any dataset to ensure we limited the analysis to incident users. The crude sequence ratio (SR) was calculated by dividing the number of persons with thyroxine initiated after amiodarone initiation with the number of persons with thyroxine initiated prior to amiodarone initiation. The SR estimates the incidence rate ratio of the event in exposed compared with non-exposed person-time. The PSSA method uses a within-person design, making it robust towards confounders that are stable over time, however, it is sensitive to prescribing trends over time. Therefore, a null-effect SR was calculated to adjust for temporal trends. The null-effect SR is the expected SR in the absence of a causal association, given the incident medicine use and events in the background population. A description of the formula used for this value is provided elsewhere. An adjusted SR was obtained by dividing the crude SR by the null-effect SR, and 95% CI was calculated. The same analyses were undertaken for amiodarone and allopurinol, as well as thyroxine and allopurinol. The PSSA analyses were restricted to sequences of

### Table 3. Prescription sequence symmetry analysis results for the association between thyroxine and allopurinol: negative control

<table>
<thead>
<tr>
<th>Country</th>
<th>N pairs</th>
<th>Thyroxine first</th>
<th>Allopurinol first</th>
<th>Adjusted sequence ratio, 95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>1092</td>
<td>519</td>
<td>573</td>
<td>0.92 (0.82–1.04)</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>215</td>
<td>105</td>
<td>110</td>
<td>0.97 (0.74–1.26)</td>
</tr>
<tr>
<td>Japan</td>
<td>47</td>
<td>31</td>
<td>16</td>
<td>1.73 (0.95–3.16)</td>
</tr>
<tr>
<td>Korea</td>
<td>933</td>
<td>471</td>
<td>462</td>
<td>1.05 (0.92–1.19)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>105</td>
<td>43</td>
<td>62</td>
<td>0.74 (0.50–1.09)</td>
</tr>
</tbody>
</table>

In the PSSA method, the date of incident dispensing of amiodarone, thyroxine, and allopurinol was determined for each individual patient. All incident dispensing that occurred within 1 year of each other for the same person were included in the analysis. We excluded patients who initiated any of the study medicines in the first year of data coverage in any dataset to ensure we limited the analysis to incident users. The crude sequence ratio (SR) was calculated by dividing the number of persons with thyroxine initiated after amiodarone initiation with the number of persons with thyroxine initiated prior to amiodarone initiation. The SR estimates the incidence rate ratio of the event in exposed compared with non-exposed person-time. The PSSA method uses a within-person design, making it robust towards confounders that are stable over time, however, it is sensitive to prescribing trends over time. Therefore, a null-effect SR was calculated to adjust for temporal trends. The null-effect SR is the expected SR in the absence of a causal association, given the incident medicine use and events in the background population. A description of the formula used for this value is provided elsewhere. An adjusted SR was obtained by dividing the crude SR by the null-effect SR, and 95% CI was calculated. The same analyses were undertaken for amiodarone and allopurinol, as well as thyroxine and allopurinol. The PSSA analyses were restricted to sequences of

![Figure 5. Temporal analysis negative control: thyroxine-allopurinol, Australia](image)

![Figure 6. Pooled analysis negative control: thyroxine-allopurinol. CI, confidence interval; SE, standard error](image)
incident dispensing within 12 months of each other to limit the effect of age and other potential time-varying covariates on the probability of exposure and outcome. Moreover, a 12-month period has better specificity and positive predictive value compared with shorter periods. Pooled estimates were obtained by using the generic inverse variance method.

RESULTS

Positive control

Prescription sequence symmetry analysis identified statistically significant associations between incident amiodarone use and subsequent initiation of thyroxine in four of the five countries, with adjusted sequence ratios ranging from 1.52 to 5.30 (Table 1). There were only limited numbers of persons dispensed amiodarone in the Japanese dataset, so while the ratio was positive, it did not reach a statistical significance. Temporal analysis showed that the observed effect of increased thyroxine dispensing was evident within a few weeks of initiation of therapy (Figure 1). This temporal association was evident in all countries (data not shown). The pooled estimate was 2.63 (95%CI 1.47–4.72, Figure 2).

Negative controls

The negative control of amiodarone and allopurinol showed no positive association in any of the countries, with adjusted sequence ratios ranging from 0.65 to 0.99 (Table 2). No temporal association was observed (Figure 3). The pooled estimate was 0.76 (95%CI 0.62–0.93, Figure 4).

For the negative control of thyroxine and allopurinol, no statistically significant positive association was observed; adjusted sequence ratios ranged from 0.74 to 1.73 (Table 3). No temporal association was observed (Figure 5). The pooled estimate was 0.98 (95%CI 0.85–1.12, Figure 6).

DISCUSSION

In this study, we found that for a known positive and two negative controls, the method produced consistent, temporally associated results across countries, despite different settings, health systems, ethnic groups, and age groups. This provides further validation of the method as a tool for signal detection across the ASPEN. One of the advantages of PSSA is that the generic enables temporal relationships to be observed, which demonstrates the strong temporal sequence for the positive control in all countries. The major limitation of the method is that it does not use diagnostic criteria, thus specific adverse events are not detected, rather medicines used to treat the adverse event are
used. This method, therefore, is reliant on the existence of a medicine that could be used to treat the symptoms of the adverse event of interest. In countries where full electronic health records are available, the method could be trialed using specific adverse events instead of a medicine indicator, for example, hospitalization events with diagnostic codes. The advantage of the method in using medicine information is that it can be used to support pharmacovigilance in many countries that routinely collect dispensing data in electronic format in an efficient manner, alongside signal detection methods from spontaneous reporting systems.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Key Points

- Prescription sequence symmetry analysis provided consistent risk estimates and temporal analyses across different data sets in different health systems for both a positive control and two negative controls.

ACKNOWLEDGEMENT

We acknowledge the contribution of Dr Tuan Nguyen in assisting with pooled estimates.

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