Application of a drug-interaction detection method to the Korean National Health Insurance claims database

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INTRODUCTION
Adverse events (AEs) by drug interactions (DIs)

- Adverse events (AEs) are a leading cause of drug-related death*
- DI accounts for 6-30% of total AEs†
- Multiple drug use in chronic patients can increase risk of drug interactions
- Detecting DIs remains challenging

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The use of post-marketing surveillance data in search of DIs

- Originally, AE case reports have been major source of AE detection
  - AE case reports are composed of AEs, drugs used, and underlying info on the patient
  - AE cases are collected and processed to be analyzed for detection of AEs
  - Have achieved a great deal in the field of pharmacovigilance*

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The use of post-marketing surveillance data in search of DIs

- Attempts have been made to use AE case reports to analyze DI
  - Calculated the AE reporting odds ratios of oral contraceptives and itraconazole*
  - Examined the effects of pairs of NSAIDs with diuretics using a logistic regression model with AE case reports†
  - Bayesian statistic model which calculates an observed-to-expected ratio‡

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Health Insurance Review and Assessment Service (HIRA)

- Obligatory health insurance system covers the Korean population
- Data of 50M are collected on a regular basis

Accumulated data is provided to researchers
Research using HIRA database

• Information on patients are recorded: drug prescription, diagnosis code, basic info, etc.
• Studies only on AE signal detection have been conducted*†
• No studies on DI have been done

*Choi, N. K., et al., 2010. Signal detection of rosvastatin compared to other statins: data-mining study using national health insurance claims database. Pharmacoepidemiology and Drug Safety. 19, 238-246
In this study

• Examined the potential of using the HIRA as a DI surveillance source
• Chose a known interaction as an example case
• Applied a method for AE case reports* to processed HIRA data
• Evaluated the application of the method to the HIRA


This research is the first attempt to use claims data as a DI surveillance resource
MATERIAL AND METHODS
DI case: NSAIDs*-Diuretics

- Administration of NSAIDs can inhibit the synthesis of prostaglandins in the kidney
- It causes sodium and water retention and hence diminish the effectiveness of diuretics
- Can have significant clinical implication in patients with predisposition to sodium retention, HF in particular

*Non-steroidal anti-inflammatory drugs

Influence of NSAIDs on the imbalance of kidney function
\( \Omega \) shrinkage measure

- Assume \( n_{111} \) follows Poisson distribution
- \( \alpha \) provides shrinkage to avoid the highlighting based on just 1 or 2 pairs

\[
\Omega^* = \log_2 \frac{n_{111} + \alpha}{E_{111} + \alpha}
\]

- \( n_{111} \): Observed value of pairs
- \( E_{111} \): Expected value of pairs
- \( \alpha \): Tuning parameter, \( \frac{1}{2} \) is used

Signal Detection by ‘Disproportionality’
Key information used

- Identification numbers (not PIN)
- Dates of hospital visits (YYMMDD)
- Dates of prescribing (YYMMDD)
- Diagnosis codes (ICD-10 coded)
- Drug codes (translated to ATC codes)
- Drug administration periods (days)
Coding AEs and drugs

- For drugs, ATC codes starting C03 and M01A were regarded as diuretics and NSAIDs respectively.
- A physician checked and revised the ICD-10 codes chosen by a pharmacist.

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>I50</td>
<td>Heart failure</td>
</tr>
<tr>
<td>I50.0</td>
<td>Right ventricular failure (secondary to left heart failure)</td>
</tr>
<tr>
<td>I50.1</td>
<td>Left ventricular failure</td>
</tr>
<tr>
<td>I50.9</td>
<td>Heart failure, unspecified</td>
</tr>
<tr>
<td>J81</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>R60</td>
<td>Edema (not elsewhere classified)</td>
</tr>
<tr>
<td>R60.0</td>
<td>Localized edema</td>
</tr>
<tr>
<td>R60.1</td>
<td>Generalized edema</td>
</tr>
<tr>
<td>R60.9</td>
<td>Fluid retention (not otherwise specified)</td>
</tr>
</tbody>
</table>

Data extraction from the HIRA

- Subjects over 17 years
- Data of insurants containing errors were excluded

Patients ever visited medical institutions during 1 Jun 2007 – 21 Jun 2007

Underlying disease

Jan 2008

Dec 2008

1-year record of them
Data preprocessing-1
- data extraction and mergence

• Outpatient records were used for drugs
• Inpatient/Outpatient records were used for diagnoses
• Merged prescription records of overlapping periods for an identical patient
• Regarded as continued medication within 20 days
• Regarded as existing diseases within 200 days
Data preprocessing-2
- generating drug-diagnosis pairs

$X_1 - X_2$: period of drug $X$ use
$Y_1 - Y_2$: period of drug $Y$ use
$Y_1 - X_2$: period of co-administration of drug $X$ and $Y$
$Z_{1-3}$: occurrence of diagnoses
Data preprocessing-3
- counting drug-diagnosis pairs

0: No NSAIDs
1: NSAIDs
0: No diuretics
1: diuretics

1: occurrence of target diagnoses
•: occurrence of any diagnosis

\[ n_{111} \]: the count of drug-diagnosis pairs of both NSAIDs and diuretics with target diagnoses
\[ n_{11} \]: the count of both NSAIDs and diuretics with all kinds of diagnoses (includes \( n_{111} \))
\[ n_{101} \]: the count of drug-diagnosis pairs of only NSAIDs with target diagnoses and so on

Bayesian approach

• A gamma prior distribution for $\mu$: $G(\alpha, \alpha)$ where $\log_2 \mu = \Omega = \log_2 \frac{n_{111} + \alpha}{E_{111} + \alpha}$

$$\int_0^{\mu q} \frac{(E_{111} + \alpha)^{n_{111}+\alpha}}{\Gamma(n_{111} + \alpha)} u^{n_{111}+\alpha-1} e^{-(n_{111}+\alpha)u} du = q$$

Logarithm of the solution for $q=0.025$:

Two sided 95% lower limit ($\Omega_{0.025}$)*

$\Omega_{0.025} > 0$ ?

Validation
- bootstrap method

• Bootstrapping was used to evaluate the accuracy and robustness of the model.

• 2,000 random draw repeats of drug-diagnosis pairs was used.

• $2.5^{\text{th}}$ percentile value of the bootstrap data, $\Omega_{\text{boot}}$, was examined.

• Check if $\Omega_{\text{boot}} > 0$.
Results – 1
- process of calculating the $\Omega$ shrinkage measure from HIRA data

Health Insurance Review & Assessment Service (HIRA)
Period from 1 Jun. 2007 to 21 Jun. 2007
13,129,115 adult insurants have visited

Exclusion of 1,565 insurants

Period from 1 Jan. 2008 to 31 Dec. 2008
13,127,550 adult insurants

575,131,274 prescription records
288,304,638 newly occurred diagnoses

862,297,889 drug-diagnosis pairs

$n_{11}^a$: 91,592
$E_{11}^b$: 76,775.99

$\Omega$ shrinkage measure: 0.255
95% lower limit of $\Omega$: 0.245

The process of calculating the $\Omega$ shrinkage measure from HIRA data
AE, adverse effect; HIRA, Health Insurance Review and Assessment Service
a Observed number of cases with the diagnoses shown in Table 1 when the records of NSAIDs and diuretics overlapped.
b Expected number of cases with the diagnoses shown in Table 1 when the records of NSAIDs and diuretics overlapped.
Results – 2  
- data for NSAIDs-diuretics interaction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>n00-</td>
<td>789,523,883</td>
</tr>
<tr>
<td>n001</td>
<td>3,937,895</td>
</tr>
<tr>
<td>n10-</td>
<td>47,613,053</td>
</tr>
<tr>
<td>n101</td>
<td>207,760</td>
</tr>
<tr>
<td>n01-</td>
<td>17,436,553</td>
</tr>
<tr>
<td>n011</td>
<td>168,935</td>
</tr>
<tr>
<td>n11-</td>
<td>7,924,400</td>
</tr>
<tr>
<td>n111</td>
<td>91,592</td>
</tr>
<tr>
<td>E111</td>
<td>76,775.99</td>
</tr>
</tbody>
</table>

Ω  
Ω_{0.025}  
Ω_{boot}  

HIRA, Health Insurance Review and Assessment Service.

CA Choi et al., Regul Toxicol Pharmacol, 67; 2013:294–298
Results – 3
- number of diagnoses by subgroups

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>NSAIDs + Diuretics</th>
<th>NSAIDs only</th>
<th>Diuretics only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of occurring</td>
<td>No./10,000 total pairs</td>
<td>No. of occurring</td>
</tr>
<tr>
<td>Heart failure</td>
<td>601</td>
<td>0.76</td>
<td>873</td>
</tr>
<tr>
<td>Right ventricular failure (secondary to left heart failure)</td>
<td>12,695</td>
<td>16.02</td>
<td>20,430</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>467</td>
<td>0.59</td>
<td>952</td>
</tr>
<tr>
<td>Heart failure, unspecified</td>
<td>7797</td>
<td>9.84</td>
<td>12,450</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1572</td>
<td>1.98</td>
<td>3081</td>
</tr>
<tr>
<td>Edema (not elsewhere classified)</td>
<td>932</td>
<td>1.18</td>
<td>2118</td>
</tr>
<tr>
<td>Localized edema</td>
<td>16,367</td>
<td>20.65</td>
<td>45,895</td>
</tr>
<tr>
<td>Generalized edema</td>
<td>11,843</td>
<td>14.94</td>
<td>23,604</td>
</tr>
<tr>
<td>Fluid retention (not otherwise specified)</td>
<td>39,318</td>
<td>49.62</td>
<td>98,357</td>
</tr>
<tr>
<td>Total diagnoses</td>
<td>91,592</td>
<td>115.58</td>
<td>207,760</td>
</tr>
</tbody>
</table>

DI, drug interaction; NSAID, non-steroidal anti-inflammatory drug.

* Total drug-diagnosis pairs of NSAID + Diuretics, NSAIDs only, and Diuretics only groups correspond to n11, n10, and n01, respectively.
Discussion

• We applied a DI-analysis method to processed HIRA data
• Calculated Ω shrinkage measure indicated that suspected DIs in the HIRA data occurred more frequently than expected
• Bootstrapping supported the result
• The disproportion corresponded to an actual interaction between the DI case
Discussion

• Not all of the ICD-10 codes reflected the actual interaction

• Seemingly obvious codes for AE cannot be appropriate codes when using HIRA data

• Choosing codes that have close and exclusive relation with AEs is essential
Advantages in using HIRA data as a DI surveillance source

• Enormous volume of data
  – A large number of cases
  – Cover almost all drugs used in Korea

• No reporting bias concerning prejudice of reporters

• Can be a complementary source
Limitations

- Application of a measure on a single DI case
- Wrong diagnostic codes may be recorded
- Drug compliance is unknown
• Application of a drug-interaction detection method to the Korean National Health Insurance claims database.

Conclusions

• We applied a drug interaction analysis model to HIRA database
• The result showed concurrence with the actual DI of the model drugs
• HIRA data have the potential to be used as a source for DI-surveillance research
• Initiation of DI analysis using claims data with a detailed method