A Comparison of Signal Detection Performance between Reporting Odds Ratio and Bayesian Confidence Propagation Neural Network Methods on Adverse Drug Reaction Spontaneous Reporting Database of the Thai FDA

Waranee Bunchuailua
Faculty of Pharmacy, Silpakorn University;
Ilene H Zuckerman
University of Maryland School of Pharmacy;
Vithaya Kulsomboon
Faculty of Pharmaceutical Sciences, Chulalongkorn University;
Wimon Suwankesawong
Thai Food and Drug Administration;
Pratap Singhasivanon
Faculty of Tropical Medicine, Mahidol University;
Jaranit Kaewkungwal
Faculty of Tropical Medicine, Mahidol University
• Primary aim of the spontaneous reporting of ADRs is to detect drug safety signals as early as possible.

• Signal is defined as “reported information on a possible causal relationship between an adverse event and a drug, of which the relationship is unknown or incompletely documented previously.”

• An association between drug and ADR is measured based on the frequency with which a particular ADR reported disproportionally with a particular drug comparing to all other drugs and ADRs in the database.
• Signal detection methods
  • Proportional reporting ratio (PRR)
  • Reporting odds ratio (ROR)
  • Bayesian Confidence Propagation Neuron Network (BCPNN)
  • Multi-item Gamma Poisson Shrinker (MGPS)

• Thai FDA uses the ROR method to screen and identify ADR signals from its spontaneous reporting database

• A comparative study of the methods needs to be explored to evaluate the performance of the methods for signal detection
OBJECTIVES

- To apply the ROR and the BCPNN methods for identifying ADR signals in the Thai FDA spontaneous reporting database
- To examine the concordance of the ROR with the BCPNN for signal detection
METHODS: SCOPE OF STUDY

- Thai FDA spontaneous reporting database between 1990 and 2006
- 272 drug-ADR pairs
  - antiretroviral therapy (ART) drugs
  - ADR (marked as critical term)
- Methods used for signal detection
  - BCPNN
  - ROR
### ROR method

<table>
<thead>
<tr>
<th></th>
<th>Reports with the ADR of interest (cases)</th>
<th>Reports without the ADR of interest (non-cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reports with drug of interest (exposed)</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Reports without the drug of interest (unexposed)</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

\[
ROR = \frac{a/c}{b/d} = \frac{ad}{bc}
\]

\[
95\% CI = \exp\left(\ln(ROR) \pm 1.96 \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}\right)
\]

a = number of reports with mention of both the drug and ADR of interest
b = number of reports with mention of the drug of interest but not the ADR of interest
c = number of reports with mention of the ADR of interest but not the drug of interest
d = number of reports with mention of neither the drug nor ADR of interest
BCPNN method

\[ E(I C_{ij}) = \log_2 \frac{(c_{ij} + \gamma_j)(C + \alpha)(C + \beta)}{(C + \gamma)(c_i + \alpha_i)(c_j + \beta_j)} \]

\[ \text{Var}(IC_{ij}) = \frac{C - c_{ij} + \gamma - \gamma_j}{(c_{ij} + \gamma_j)(1 + C + \gamma)} + \frac{C - \alpha + \alpha - \alpha_i}{(c_i + \alpha_i)(1 + C + \alpha)} + \frac{C - c_j + \beta - \beta_i}{(c_j + \beta_j)(1 + C + \beta)} \]

\[ \gamma = \gamma_j \frac{(C + \alpha)}{(\alpha + \alpha_i)} \cdot \frac{(C + \beta)}{(\beta + \beta_i)} \]

\[ \gamma_{ij} = 1, \alpha_i = 1, \alpha = 2, \beta_j = 1, \beta = 2 \]

C is the total number of reports in the database

\( c_{ij} \) is the number of reports of a specific drug \((i)\) and the ADR \((j)\)

\( c_i \) is the number of reports of a specific drug in the database

\( c_j \) is the number of reports of a specific ADR in the database
METHOD: DATA ANALYSIS

272 drug-ADR pairs (stavudine – rash)

Cumulative frequency (number of reports) of reporting at quarterly time interval

ROR

Signal identified when ROR > 1, case reports ≥ 3, lower limit ROR > 1

Number of signals

BCPNN

Signal identified when IC – 2SD > 0

Number of signals

Measure the concordance between the two methods

Sensitivity  Specificity  Timing of signal detection
Nevirapine-hepatitis

Information component (IC)

- IC
- IC-2SD
- IC+2SD

Reporting odds ratio (ROR)

- ROR
- Lower95% CI
- Upper95% CI

Time (year/quarter)
# Sensitivity/Specificity Analysis

<table>
<thead>
<tr>
<th></th>
<th>Detected by BCPNN</th>
<th>Not detected by BCPNN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected by ROR</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Not detected by ROR</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>N = a+b+c+d</td>
</tr>
</tbody>
</table>

- **Sensitivity** = \( \frac{a}{a+c} \)
- **Specificity** = \( \frac{d}{b+d} \)

- **a** = number of signals detected by both methods
- **b** = number of signals detected by the ROR method only
- **c** = number of signals detected by the BCPNN method only
- **d** = number of signals detected by neither the ROR nor the BCPNN

\( N = a+b+c+d \)
**AGREEMENT OF TIMING OF SIGNAL DETECTION**

Signals detected by both methods

Evaluate the first time of signal detection

Both methods detected at the same time

ROR detected earlier than BCPNN

BCPNN detected earlier than ROR

Percent agreement

\[
\text{Percent agreement} = \left(\frac{\text{number of signals detected at the same time}}{\text{total number of signals detected by both methods}}\right) \times 100
\]
• Sensitivity and Specificity

<table>
<thead>
<tr>
<th></th>
<th>Detected by BCPNN</th>
<th>Not detected by BCPNN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected by ROR</td>
<td>105</td>
<td>6</td>
<td>111</td>
</tr>
<tr>
<td>Not detected by</td>
<td>0</td>
<td>161</td>
<td>161</td>
</tr>
<tr>
<td>the ROR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>167</td>
<td>272</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{105}{105 + 0} = 1 \)

Specificity = \( \frac{161}{161 + 6} = 0.96 \)
• ROR method was highly sensitive and specific for detecting ADR signals in the Thai FDA database.

• The number of reports of a drug-ADR pair was likely to have high impact on differences between the tests.

• BCPNN detected fewer signals for drug-ADR pair with two or three case reports, this may explain by the use of Bayesian statistics can reduce the fluctuation of IC with small report count.
RESULTS (Cont.)

- Agreement of timing of signal detection
  - 130 signals detected by both methods
  - 100 signals were found to be identified at the same time by both methods
  - 28 signals were detected by the ROR earlier than the BCPNN
  - 2 signals were detected by the BCPNN earlier than the ROR

\[
\text{Percent agreement} = \frac{100}{(100 + 28 + 2)} \times 100 = 76.92\%
\]
• Most signals detected by the ROR and the BCPNN agree on the first time of signal detection.

• ROR detected signals earlier than the BCPNN.

• The calculation of ROR values cannot be performed in some quarters since there are no other drugs reported with ADR of interest and also no other ADRs reported for drug of interest during that time while the IC was calculated.
CONCLUSION

• The ROR can identify ADR signals for ART drugs when applied to the Thai FDA spontaneous reporting database between 1990 and 2006

• The ROR method can detect ADR signals in concordance with the BCPNN method
Presenter received financial support from the Thai Health Global Link Initiative Project (TGLIP) through the Health Intervention and Technology Assessment Program (HITAP)
QUESTIONS ?