ROBUSTNESS OF THE CPA-PRR METHOD IN PHARMACOVIGILANCE DETECTION

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INTRODUCTION

Pharmacovigilance signal detection commonly utilizes time-invariant disproportionality analysis methods and rarely capitalizes on time dependency (1, 2). The time-series analysis tool, change-point analysis (CPA), is a powerful method to analyze surveillance data (3, 4).

CPA was applied for the first time in Pharmacovigilance and demonstrate is interest by combining with dynamic Proportional Reporting Ratio (PRR) (5).

The signaling criteria in the CPA-PRR method defines a substance-event as a potential signal when the two following criteria are fulfilled: PRR- is greater than 1 with at least 5 cases, the time series analysis with CPA detects at least two successive change points of PRR- and increasing values of those detected points (5).

We aimed to evaluate the robustness of CPA-PRR method for optimizing pharmacovigilance signal detection.

METHOD

Study: retrospective analysis

Data: computed monthly PRRs with their 95% confidence interval until July 2016 extracted from the Eudravigilance database (EV)

Test cases: Ustekinumab - Dermatitis exfoliative, Aripiprazole – Hyperprolactinaemia, Temozolomide - Diabetes insipidus

Outcome measure: lower bound of PRR (PRR-)

CPA method: Taylor *et al.* (2000), Change-Point Analysis: A Powerful New Tool For Detecting Changes

RESULTS

We tested the CPA in combining with PRR on the test case of Aripiprazole and Hyperprolactinaemia. From June 2005 until July 2016, 47 cases had been reported to EV. Based on this data, this couple can be detected as a SDR in December 2006 which also presented a significant change in the PRR-. During this period, 11 changes were detected when analysing the PRR- and after December 2006, we observed 3 consecutive upward segments (Table 1). This issue was addressed by PRAC in August 2014.

Similarly with Temozolomide and Diabetes Insipidus, 24 cases had been reported to EV from October 2004 to July 2016. This signal fulfilled SDR requirement in September 2011. CPA method detected 23 changes in the PRR-. After September 2011, we observed two upward segments. This issue was addressed in April 2014.

However, Ustekinumab - Dermatitis exfoliative can be detected by CPA-PRR in June 2015 while this issue was already addressed by PRAC in August 2013

Table 1. Change points detected by Change Point Analysis when analysing the lower bound of the Proportionality Reporting ratio of Aripiprazole and Hyperprolactinaemia using Eudravigilance data

No.	Change point	Confidence level[1]	Level [2]	Interval before the change point	Interval after the change point	% Difference [3]	Trend [4]
1	12/2005	99.9	3	1.02	2.52	145.93	Moderately upward
2	06/2006	99.6	4	2.52	1.82	-27.68	Moderately downward
3	**12/2006**	**100.0**	**2**	**1.82**	**2.37**	**30.20**	**Moderately upward**
4	04/2009	99.8	3	2.37	2.76	16.33	Moderately upward
5	10/2009	100.0	1	2.76	3.77	36.94	Moderately upward
6	08/2010	99.4	5	3.77	3.61	-4.40	Moderately downward
7	04/2011	100.0	4	3.61	3.43	-4.90	Moderately downward
8	09/2011	99.7	5	3.43	3.19	-7.18	Moderately downward
9	04/2012	95.0	6	3.19	3.48	9.24	Moderately upward
10	05/2012	100.0	3	3.48	3.79	8.80	Moderately upward
11	04/2013	100.0	2	3.79	4.18	1.,30	Moderately upward

(1) Confidence level is calculated as the percentage of bootstraps for which $S^0_{diff} < S_{diff}$ in the total bootstraps performed.

(2) Level indicates the number of iterations in the CUSUM computation procedure, where level n means the CUSUM run on each segment after splitting the total time series from change points at previous levels. The level values show the order of change points detected since CUSUM is an iterative procedure.

(3) % difference (Δ) is computed as the difference in mean of the monthly count between the interval after the change point and the interval before the change point.

(4) Trends are defined as: moderately up (Δ >1%), slightly up (0<Δ≤1%), slightly down (-1%< Δ≤0) and moderately down (Δ≤-1%).

CONCLUSION

Our preliminary results on CPA-PRR method demonstrated its robustness in the early detection of pharmacovigilance signals. The proposed method could be applied in combination with disproportionality analysis in Pharmacovigilance signal detection after further investigations.

Conflicts of interest

No conflicts of interest to declare by authors.