THE APPLICATION OF SIGNAL DETECTION IN TAIWAN NATIONAL ADVERSE DRUG REACTION REPORTING SYSTEM : METFORMIN-ASSOCIATED LACTIC ACIDOSIS (MALA) AS AN EXAMPLE

Background

In 2008, 7 death cases were reported with suspected metformin–associated lactic acidosis (MALA) via Taiwan National Adverse Drug Reaction (ADR) Reporting System. Then, traditional signal detection approach led us to re-evaluate the safety of metformin use and further implemented drug labeling changes at that time.

Signal detection is a way used widely for screening the potential risk of drug use in the field of pharmacovigilance. Recently, more complex methods have been introduced to enhance the capabilities of analyzing large volumes of data.

Objective

This retrospective analysis is to determine whether the automated quantitative signal detection method could be useful in detecting clinically meaningful signals in advance.

Method

Data had been collected from 2002 to 2010 by Taiwan National Adverse Drug Reaction (ADR) Reporting System. A disproportionality analysis by calculating proportional reporting ratio (PRR) on annually accumulated was performed in metformin-lactic acidosis combination.

Cases with Lowest Level Term (LLT) level under lactic-acidosis category of Standardised MedDRA Query (SMQ) version 14.0 were included. The Coefficient of variation (CV) of PRR was also calculated. Once the signal had emerged, the patients' characteristics of MALA cases were reviewed and compared.

Result

The PRR ranged from 241 to 486 and the CV of PRR ranged from 16.4% to 3.7% from 2002 to 2010.(**Table 1.**) The variation of PRR decreased over time and has tended to be stable since 2005 (311, 95%CI[142-678], CV=6.9%).

Table 1. PRR for metformin-associated lactic acidosis(MALA)[a]

Year	MALA NO.	PRR	95%C.I. Lower limit	95%C.I. Upper limit	CV(%)[b]
2002	3	241.5	41.6	1402.0	16.4
2003	7	310.8	94.3	1024.7	10.6
2004	11	252.6	101.1	631.1	8.4
2005	17	310.7	142.5	677.7	6.9
2006	25	358.0	180.3	710.7	6.0
2007	33	394.1	206.9	750.4	5.5
2008	50	455.5	259.3	799.9	4.7
2009	70	429.8	269.6	685.0	3.9
2010	83	486.1	309.7	762.9	3.7

a Suspected ADRs under lactic-acidosis category of Standardized MedDRA Query (SMQ) version 14.0
b Coefficient of variation

Since the potential risk might be identified in 2005, we compared the patients' characteristics of MALA cases before 2005 with those in 2008. Total of 17 cases were reported in each groups (before 2005 versus 2008).

All cases were hospitalized, but no death case reported before 2005 comparing to 7 death cases reported in 2008. Cases in these two groups had same mean age (68.2±10.56 v.s. 68.1±10.16, years) and used similar dosing regimen. The similar predisposing factors of MALA were also found in both groups, including renal dysfunction (82% v.s. 94%; [Scr], 5.91±2.34 v.s. 4.88±3.4, mg/dl), infection (41% v.s. 59%), hepatic dysfunction (18% v.s. 35%).(**Table 2.**)

It suggested that patient in MALA cases shared similar characteristics in two groups. Therefore, discovery of this issue by PRR method cloud be done earlier and should have be able to mitigate the risk of developing MALA for patients taking metformin.

Table 2. . Characteristics of cases with suspected MALA

Year	Before 2005	2008	p-value
Cases---n	17	17	
Gender---n (%)			0.8942
Male	6(35%)	12(71%)	
Age---mean±S.D.	68.2 ± 10.56	68.1 ± 10.16	0.9738
Scr--mean±S.D.	5.91* ± 2.34	4.88** ± 3.4	0.277
Predisposing Factor---n (%)			
Renal dysfunction	15(82%)	16(94%)	0.9991
Chronic kidney disease	8(47%)	7(41%)	0.9999
Replacement therapy	3(18%)	2(12%)	0.9999
Acute renal failure	11(65%)	15(88%)	0.9776
Heart failure	3(18%)	0(0.0%)	0.9517
Hepatic disorder	3(18%)	6(35%)	0.998
Sepsis	7(41%)	10(59%)	0.9992
Shock	1(6%)	1(6%)	
Alcohol abuse	0(0.0%)	3(18%)	0.9517
Lactate--mean±S.D.	25.69# ± 7.4	19.62#, ## ± 9.56	0.277
Outcome---n (%)			
Death	0(0.0%)	7(41%)	0.4545
Life-threatening	3(18%)	1(6%)	0.999
Hospitalization	7(41%)	5(29%)	0.9999
Prolonged hospitalization	1(6%)	0(0.0%)	0.9994
Require intervention to prevent permanent impairment or damage	2(12%)	2(12%)	0.9998
Others	2(12%)	2(12%)	

*n=14 ; **n=15 ; #n=9 ; ##n=16

Conclusion

MALA cases in our database shared similar profiles. PRR methods could be a useful tool to assist in detecting signals.

Reference

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