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FREQUENTLY ADVERSE DRUG REACTIONS OF METFORMIN AND CHARACTERISTICS OF LACTIC ACIDOSIS DOCUMENTED FROM METFORMIN: ANALYSIS FROM THAI NATIONAL PHARMACOVIGILANCE DATABASE.

Phitsouda Komthamixay[1,2], Wimon Suwankesawong[3], Pakawadee Sriphiromya[3], Sareeya Wechwithan[3]

[1] Master II Mékong Pharma, spécialité en médicament et santé publique.
[2] Food and Drug department, Ministry of Health Laos.
[3] Health Product Vigilance Center (HPVC), Food and Drug Administration, Ministry of Public Health, Thailand.

Abstract

Background: Metformin is one of the most widely used oral anti-diabetic drug currently considered to be one of the first choice drug for type 2 diabetes mellitus (T2DM). However, some mostly occurred adverse drug reaction (ADRs) and serious ADR of metformin as Lactic acidosis (LA) were frequently observed.

Objective: This study is aimed to describe the frequently adverse drug reactions (ADRs) of metformin and characteristic of Lactic acidosis (LA) documented from metformin in Thai national Pharmacovigilance database.

Methods: A descriptive retrospective study using the National Pharmacovigilance database of Thailand. Spontaneous report of ADRs documented from metformin since 1984 until 06 July 2016 were collected and extracted by quality of report and causality assessment. Characteristics of reports, top 10 ADRs and characteristics of LA documented from metformin were analyzed descriptively regarding the report content.

Results: A total of 2,013 reports are identified and analyzed descriptively. Mean age was 51.0±12.1 years old and 75.2% being Female. 516 reports (25.6%) presented co-morbidity. Almost were 1-2 items of concomitant drugs used (75.6%). Causality assessment was mostly classified as probable (60.3%) with quality of report graded at quality level 2 (54.7%). The number of suspected ADRs reports to Metformin since 1984 to 06 July 2016 are slowly

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increased by time. The most ADRs documented from metformin were skin rash (9.2%) and pruritus (8.7%). Characteristics of LA recognized fromm metformin almost were female (62%) with mean(±SD) age 62.5±12.7 years old. Enalapril was the most implicated drug (21%), followed by Glipizide (10%) and 88% were classified as serious event.

Conclusion: In Thai database, the most frequent ADRs documented from metformin was skin and appendages disorders. Female, the higher age and use of Enalapril was the most documented in LA reports form metformin. Therefore, present descriptive study may aid medical professional to prevent the possible occurrence of ADRs to the patients.

Introduction

Metformin is one of ancient antidiabetics drug which full of various benefits as efficacy of lowering blood glucose level, safety profile, benefic cardiovascular, metabolic effect and capacity to be associated with other antidiabetic agents. Those therefore makes this drug was recommended as a current first-line drug pharmacological for Type 2 Diabetes Mellitus (T2DM) in adults and was on the World Health Organization's List of Essential Medicines; the most important medications needs in a basic health system.[1, 2] Metformin is currently approved as registered drug and most prescribed in many countries under various trade names. Total 153 formulas (146 for single formulas and 7 for combination formulas) were registered in Thailand.

The quite frequent adverse drug reactions (ADRs) of this drug were gastrointestinal symptom such as nausea, vomiting, abdominal pain, flatulence, diarrhea and loss appetite. Other less frequent were skin reactions, decreased B12 absorption and weakness. The rarely one but serious was Lactic acidosis (LA), which called Metformin associated with Lactic acidosis (MALA).[3, 4]

This classic but severe side effect was a life-threatening condition which characterized by low arterial pH (<7.35) and elevated arterial lactate levels (>5mEq/l).[5] This critically illness usually was observed in individual with poor renal functions (i.e., reduced Metformin clearance), impaired hepatic metabolism (reduced lactate clearance) and/or in the presence of increased production (i.e., septic, congestive heart failure (CHF), reduced tissue perfusion or anoxia). The mortality associated with this rare adverse drug effect is 50% with all biguanides. However, this absolute risk has proved to be very low with Metformin (<10 cases per 100,000 patient-years).[4]

Most contraindications, special warnings and precautions for use labelled in the metformin summary product characteristics are aimed at minimizing this risk. Recently, contraindications have been judged unjustified and too restrictive. Moreover, the risk in patient without contraindications is unknown and in all likelihood negligible. Therefore, these ADRs were frequently observed especially LA in who at risk such as insufficient renal patients. Thus, this study is aimed to describe the frequently occurring ADRs of Metformin and the characteristic of LA documented by metformin in Thai pharmacovigilance database.

Methods

Data source This descriptive retrospective study collected data from 1984 until 6 July 2016 from health product Vigilance Center (HPVC) database (called "Thai Vigibase"), the national

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pharmacovigilance database of Thailand. Thai Vigibase is under the direct supervision of HPVC which was established in 1983 under the Thai Food and Drug Administration, Ministry of Public Health (http://thaihpvc.fda.moph.go.th). The HPVC has been collecting and managing case reports submitted from Spontaneous Adverse Event reporting systems, intensive monitoring programs, and clinical trials nationwide since 1984. The reported drugs were enrolled as WHO-Anatomical Therapeutic Chemical classification system code (ATC code). Likewise, all reported ADRs were recorded as WHO-International Adverse Reactions Terminology (WHO-ART Classification). Furthermore, the assessment for the quality of report was done by HPVC using the modified WHO-Uppsala Monitoring Center (WHO-UMC) document grading. [6] Currently, HPVC has more than 900 network of public and private hospitals, health service center and now contain approximately 700,000 annually from the nation.[7]

Inclusion Criteria_The reports that were included in this study had to be any spontaneous Adverse Drug Reactions (ADRs) reports from metformin documented as a suspected drug (ATC code: 'A10BA02', 'A10BD08').

Data Extraction_All included reports have to identify unique HPVC number, a detail information of basic patient's demographic, ADRs, co-morbidities, History of allergies drug, and concomitant drugs. All ADRs including serious ADR of Metformin like Lactic acidosis (LA) in this study were defined by causality assessment as "certain", "probable" and "possible" along Health professionals carried out at the time of report submission with document grading level 0,1,2,3.

Exclusion Criteria_All reports that got the quality of report grading 9 with causality assessment as "Unlikely" and "Unclassified" were excluded.

Data management_Relevant data were firstly selected for Metformin as a suspected drug, selected data was then extracted for causality assessment and quality of report grading. These included data were removed duplicate of HPVC number and analyzed Descriptively regarding the report content. Top 5 of body system and ADRs which most documented from metformin were collected to describe.

Statistical analysis_Descriptive statistics were used to describe baseline characteristics of reports. The number of ADRs suspected to metformin and LA affected from metformin were explained by pivot chart. Percentage of each ADRs and characteristics of LA due to Metformin treatment as Mean ± SD of age, use of concomitant drug, history of allergies, seriousness of LA and outcome after treatment were also analyzed descriptively.

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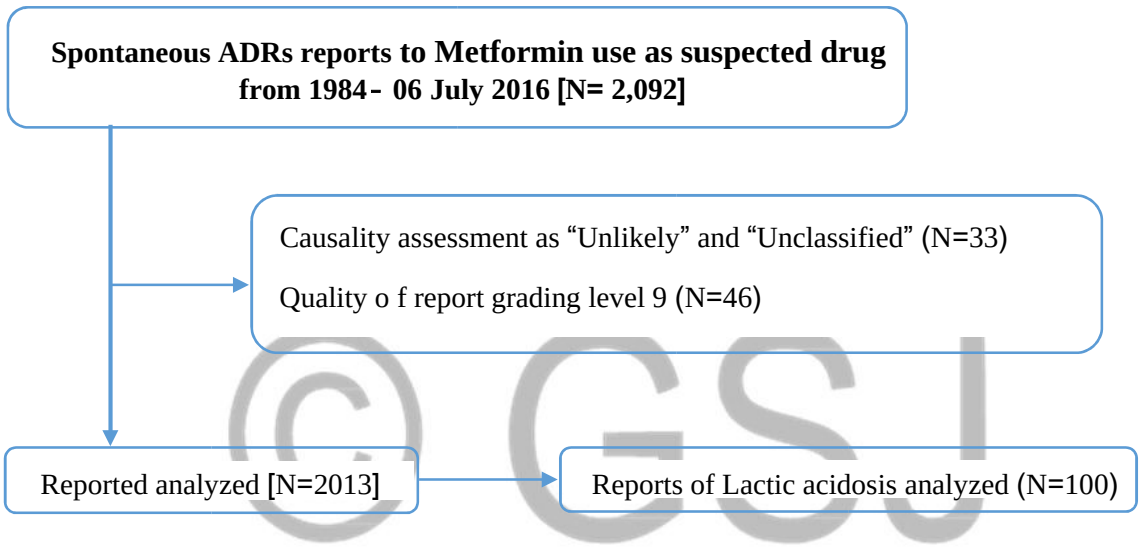
Results

A total of 2,092 spontaneous ADRs reports to Metformin use as suspected drug from 1984 to 06 July 2016 were collected from the HPVC database. 79 reports were excluded; 33 for causality assessment as Unlikely and Unclassified; and 46 for quality of report grading level 9. Therefore, 2,013 reports were included and analyzed in this study.



Among 2,013 reports, age range from 11-94 years, 50-59 years (28.7%) was a majority of report, as compared with 60-69 years (24.5%) with mean(±SD) age of 51.0±12.1. Female was the relevant gender (75.2%). There were 516 reports (25.6%) presented co-morbidity, 3 of these 516 reports presented chronic kidney disease which were severe cases with lifethreatening and requires inpatient and prolong hospitalization. Almost, there were used 1-2 items of concomitant drugs (75.6%). History of drug allergies was documented 158 cases (7.8%). Causality assessment was mostly classified as probable (60.3%). Regarding the quality of reports, most were graded at quality level 2 (54.7%) (Table 1).

Table 1: Characteristics of reports

Parameter	Number of reports [N] (%)	
Age (Years)		
Mean	57.0±12.1	
<20	5	0.2
20-29	19	0.9
30-39	103	5.1
40-49	370	18.4

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50-59	578	28.7
60-69	493	24.5
>70	293	14.6
Not reported	152	7.6
Gender		
Female	1513	75.2
Male	497	24.7
Not reported	3	0.1
Co-morbidities		
Yes	516	25.6
No	1369	68.0
Not reported	128	6.4
Use of concomitant drug		
1-2 items		
3-5 items		
>5 items		
None		
History of drug-allergies		
Yes	158	7.8
No	1510	75.0
Not reported	345	17.1
Causality assessment		
Certain	153	7.6
Probable	1214	60.3
Possible	624	31.0
Not reported	22	1.1
Quality of reports [a]		
Quality 0	68	3.4
Quality 1	623	30.9
Quality 2	1102	54.7
Quality 3	220	10.9

[a] World Health Organization-Uppsala Monitoring Center (WHO-UMC) documentation grading

Figure. 1 showed the expanding of ADRs reports which documented from metformin. Initial form 2-9 reports during 1993-1996, there were much increased to 27-89 reports in 1997-2008 and 138-197 reports in 2009-2014.

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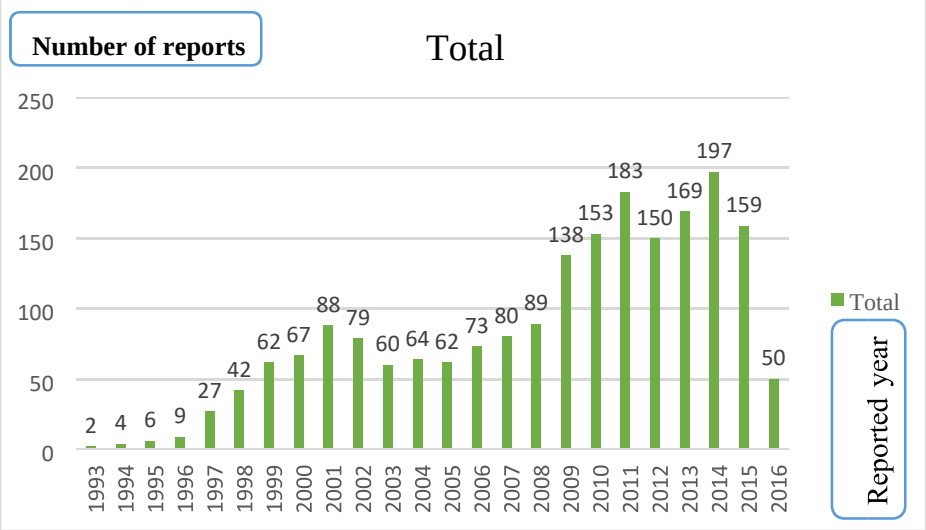

Figure 1: Number of suspected ADRs reports to Metformin since 1984 to 06 July 2016.

Table 2: Mostly Adverse Drug Reactions affected by Metformin

Body systems	Type of Adverse Drug Reactions	Number of Reports [N] (%)
SKIN AND APPENDAGES DISORDERS	Skin rash	186 (9.2)
	PRURITUS	175 (8.7)
	URTICARIA	126 (6.3)
	RASH MACULO-PAPULAR	123 (6.1)
	RASH ERYTHEMATOUS	40 (2.0)
	ANGIOEDEMA	40 (2.0)
AUTONOMIC NERVOUS SYSTEM DISORDERS	DIARRHOEA	124 (6.2)
	VOMITING	119 (5.9)
	PALPITATION	59 (2.9)
	ANOREXIA	57 (2.8)
	MOUTH DRY	7 (0.3)
METABOLIC AND NUTRITIONAL DISORDERS	ACIDOSIS LACTIC	100 (5.0)
	HYPOGLYCAEMIA	99 (4.9)
	ACIDOSIS METABOLIC	32 (1.6)
	OEDEMA	13 (0.6)
	OEDEMA LEGS	6 (0.3)

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CENTRAL & PERIPHERAL NERVOUS SYST. DISORDERS	DIZZINESS	126	(6.3)
	HEADACHE	32	(1.6)
	VERTIGO	9	(0.4)
	NUMBNESS	3	(0.1)
	ANAESTHESIA LOCAL	2	(0.1)
GASTRO-INTESTINAL SYSTEM DISORDERS	NAUSEA	49	(2.4)
	ABDOMINAL PAIN	20	(1.0)
	FLATULENCE	18	(0.9)
	ABDOMINAL DISCOMFORT	11	(0.5)
	DYSPEPSIA	8	(0.4)

Table 2 showed the list of ADRs documented in 2,013 reports due to metformin use. This table clearly showed that skin and appendages disorders such as skin rash (9.2%), pruritus (8.7%) and urticarial (6.3%) were mostly reported ADRs from metformin, followed by dizziness (6.3%), diarrhea (6.2%) and vomiting (5.9%). Other then, Lactic acidosis (LA) (5%) and hypoglycemia (4.9%), the serious ADRs were also reported in certain majority of report.

It is well known that the serious ADR of metformin was LA, Figure 2 therefore showed the number of LA since initial reported until 06 July 2016. These reports were increased with time which much growth in 2013, followed by 2014 and 2015, there were 13; 14 and 24 reports, respectively.

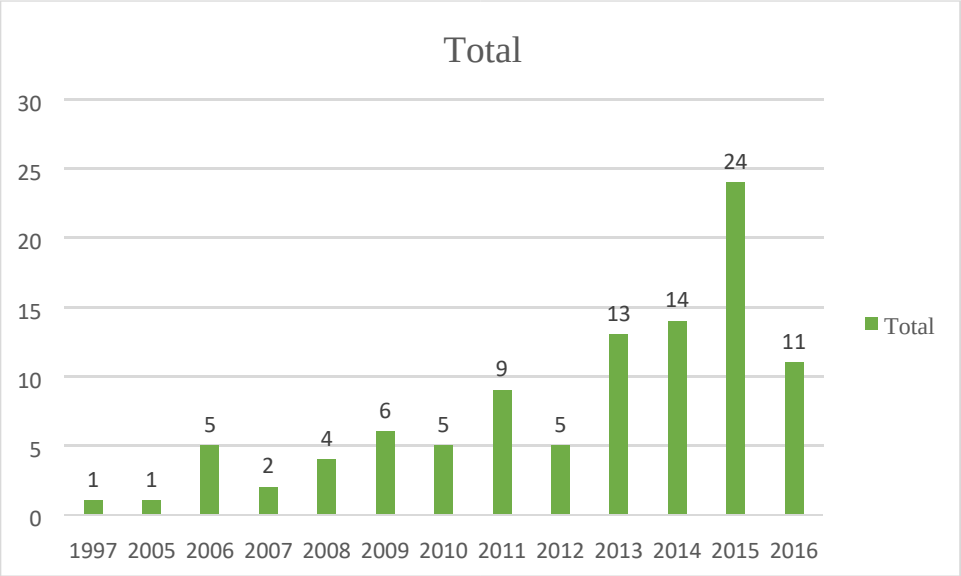

Figure 2: Number of LA reported due to Metformin use since 1984 to 06 July 2016.

Characteristics of LA, the serious ADR of Metformin were described in Table 3. The higher age groups as 60-69 (25%); ≥70 (22%) and 50-59 (20%) years old were the groups

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mostly reported of LA. These were most to be Female (62%). Among the concomitant drug, the top five of most common implicated drug with LA in this study were Enalapril (21%), Glipizide (10%), Glibenclamide (9%), Hydrochlorothiazide (9%) and Amlodipine (8%). A total of 100 reports, 79 reports (79%) were documented as don't have the history of allergies and 47% was recovered without sequelae. However, the majority of reports was classified as serious (88%). Among those with serious events, 13% were life-threatening and 71% required either inpatients and prolonged hospitalization with recovered without sequelae 47%. Overall, there were 3 dead cases, 2 of these dead due to ADRs and the other one could not be followed the cause.

Table 3: Characteristic of LA affected by metformin treatment.

Parameter		Number of Reports (%) [N=100]	
Age (Years)			
	Mean	62.5±12.7	
	□20	0	0
	20-29	1	1
	30-39	1	1
	40-49	12	12
	50-59	20	20
	60-69	25	25
	≥70	22	22
	Not reported	19	19
Gender			
	Female	62	62
	Male	38	38
Use of concomitant drugs a			0
	Enalapril	21	21
	Glipizide	10	10
	Glibenclamide	9	9
	Hydrochlorothiazide	9	9
	Amlodipine	8	8
History of allergies			
	Yes	2	2
	No	79	79
	Not reported	19	19
Seriousness of events			
	Non-serious	9	9
	Serious	88	88
	Death	3	3
	Hospitalization-initial or prolonged	71	71
	Life-threatening	13	13
	Not available	1	1

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Not reported	3	3
Outcomes after treatment		
Death	2	2
Loss of follow up	6	6
Not yet recovered	28	28
Recovered without sequelae	47	47
Recovered with sequelae	8	8
Recovering	9	9

[a] Each case may have >1 Concomitant drugs

Discussion

Findings from this study provided base information relevant the safety of metformin treatment in developing country by compared with existing information and previous studies from western countries. Results from this study was contrasted to previous studies showed that the most of Patients treated with Metformin was 50-59 years old with Mean (±SD) 57.9 ± 12.01 years old. [8-10] This could be explained by the onset of type 2 diabetes in Thailand after the age of 50 points toward a rise in the disease burden. [11] Although, our based results were accorded with those studies and *Michael Bodmer et al, 2008* suggested that Female was most implicated gender.[12] In addition, current study found that the number of ADRs reports from Metformin was rise together increasingly of metformin use. [13]

Possible forasmuch that skin disorder was a clinical which easy to detect. Thus, this finding showed that skin and appendages disorders such as skin rash, pruritus and urticarial were mostly ADRs occurred from metformin, which was contrasted with some previous studies implying that diarrhea and the occurrence of hyperacidity and flatulence were most frequent occurred in patients treated with metformin [14, 15] Other than, the study design was may also different. [16] Although, the principally occurred ADRs of metformin in present study were accorded to various studies and published. [1,14,15] Additionally, present study was found that the reports of serious ADRs as Lactic acidosis was trend to be growing by time together increasingly of Metformin treatment.

As showing in the figure. 2 that LA reports were much increasing in 2013. Probably due to underreporting, the percentage of LA reports in this study (nearly 5% or 100 reports of all 2013 reports documented from metformin) was lower than 18.2% which indicated from *F. Renda et al, 2013*. [10]. Present study was consisted with prior studies indicating that female was a group which implicated with LA, because the majority of Type 2 DM and metformin using was Female. Other than, current study was agreed to previous studies showing that the higher age was the risk factors associated with LA and as according to some prior studies implying that Enalapril was most implicated drug which could develop LA in use of metformin. [8, 17-20] Furthermore, this results constantly found that the occurrence of LA was always a

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serious event with life-threatening, required to inpatients or prolong hospitalization and sometime fatal. [10, 21, 22]

Several limitations exist in current study, due to underreporting of ADRs was one of the major issues of HPVC database, so this study unable to identify the stage of CKD and risk behaviors such as Alcohol drink which were documented as risk factors associated with occurrence of LA among Metformin users. In the other side, the limited quality of reports, especially incomplete data might also effect to this study. Nevertheless, the based result regarding ADRs affected from Metformin treatment give us ability to perform comparative analysis with similar data from other Western countries. Besides, a clear trend for increasing number of LA reports in this finding might suggest exponential growth of improvement the compliance of spontaneous report toward the wariness in prescribing of healthcare professional for special patients.

Conclusion

Current study indicated that the most frequent ADRs documented from metformin was skin and appendages disorders. Female, the higher age and use of Enalapril was the most documented in LA reports form metformin. Therefore, present descriptive study may aid medical professional to prevent the possible occurrence of ADRs to the patients. Until more data available, it is interested for further investigated and validated studies regarding the safety of metformin treatment in developing Asian country to minimize the risk which rare yet potentially increasing continuously.

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