Potential Drug Interactions Of Oral Antidiabetic In Prescriptions Of Type 2 Diabetes Mellitus Patients At Kumpulan Pane Hospital

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Abstract.
Diabetes Mellitus is a disease that can cause complications of other diseases so that the treatment to be given becomes more and this has the potential for interactions between drugs that can affect the physiological condition of the patient. The aim of this study is to analyze the potential of oral antidiabetic interactions on prescription at Kumpulan Pane Hospital. Analysis of potential oral antidiabetic interactions on a prescription using quantitative research methods is retrospective descriptive. Prescriptions used are inpatient and outpatient prescriptions for the period January-December 2020 that get oral antidiabetics. Analyze data using Medscape and Drugs.com sites. Based on analysis of 9.818 prescription sheets of diabetes mellitus patients, there were found 6.454 (65.73%) prescription of potential oral antidiabetic interactions. Potential interaction of an oral antidiabetic group of 10.759 (91.45%) drug, the pattern of interaction mechanisms most often is pharmacodynamic 73.25%. The most common type of oral antidiabetic drugs that have potential interactions is the biguanide group (metformin) 36.76%. The severity of the most frequent interactions was 92.21%. The conclusion of the potential interactions oral antidiabetic are still found in prescriptions that is 65.73% at Kumpulan Pane Hospital.

Keyword: *Potential Drug Interactions, Oral Antidiabetics, Prescription*

I. INTRODUCTION

Diabetes mellitus (DM) is a disease characterized by the occurrence of hyperglycemia and impaired metabolism of carbohydrates, fats, and proteins associated with absolute or relative deficiencies of work and or secretion of insulin [1]. Diabetes mellitus is also one of diseases that have a high potential to cause the emergence of other diseases that cause the administration of various drugs that can facilitate the occurrence of drug interactions [2].

Diabetes mellitus patients with a history of concomitant diseases then the treatment to be given becomes more and this has the potential for interactions between drugs that can affect the physiological condition of the patient [3].Hospitals as one of the health facilities that provide and organize health efforts that are healing and recovery of patients monitored by doctors play a big role in the incidence of drug interactions in patients. In general, inpatients and outpatients who are in the hospital get a variety of medications, be it orally or injection. So the possibility of interaction between drugs also increases [4].

II. METHOD

Research using quantitative methods. Quantitative research methods is retrospective descriptive used in the analysis of potential oral antidiabetic interactions on prescription. Inclusion criteria are prescriptions that get oral antidiabetics in outpatients and inpatients in the period January – December 2020 at Kumpulan Pane Hospital, Tebing Tinggi and exclusion criteria are prescriptions that do not get oral antidiabetics. Quantitative data was analyzed using Medscape and Drugs.com to determine the frequency of drug interactions, interaction mechanisms, types of oral antidiabetics that often interact, and the severity of interactions.

III. RESULTS AND DISCUSSION

Analysis of Potential Oral Antidiabetic Interactions In Prescriptions of Patients with Type 2 Diabetes Mellitus

3.1.1 Potential Drug Interactions Of Patients with Type 2 Diabetes Mellitus

Total oral antidiabetic prescription obtained as many as 9.818 sheets that into the inclusion criteria. Based on **Table 1**, the potential oral antidiabetic interactions occurred at 6.454 (65.74%) recipe. **Table 1** describes that the potential for more drug interactions occurred in patients receiving ≥5 drugs 3.093 (31.50%) recipe. This is because in addition to getting more prescriptions in patients who get ≥5 drugs also because basically, patients who use more drugs will be more likely to experience interactions. In addition, due to the increasing use of drugs resulting in interactions between drugs-drugs in the body are getting bigger which results in affecting the effects of therapy. Drug interactions based on the number of drugs the higher the number of drugs prescribed the increasing drug interactions [5]. The following are the results of the analysis of potential drug interactions in diabetes mellitus type 2 patients (**Table 1**).

Table 1. Potential Drug Interactions of Patients with Type 2 Diabetes Mellitus

Subject Characteristics	Total DM Patient Prescription Sheet (n = 9.818)	
	Interact	Not Interacting
Number of Drugs:		
a. Two Medicines	876 (8.92%)	97 (0.99%)
b. Three Drugs	1.009(10.28%)	2.111 (21.50%)
c. Four Drugs	1.476(15.03%)	872 (8.88%)
d. ≥ Five Medicines	3.093(31.50%)	284 (2.89%)
	6.454 (65.74%)	**3.364 (34.26%)**
a. No Concomitant Diseases	876 (8.92%)	97 (0.99%)
b. With Concomitant Diseases	5.578 (56.81%)	3.267 (33.23%)
	6.454 (65.74%)	**3.364 (34.26%)**

Based on **Table 1** shows the potential for more drug interactions in patients with concomitant diseases 5.578 (56.81%) recipe. This is because the use of drugs in patients who have a history of concomitant diseases is more because in addition to treating major diseases, doctors also treat other diseases suffered by patients, resulting in a large number of drugs given. And the more drugs used, the more likely the potential drug interactions are. In addition, often doctors provide medication based on the symptoms complained by the sufferer without considering the importance or absence of symptoms faced, thus facilitating the occurrence of drug interactions [2].

3.1.2 Analysis of Potential Drug Interactions Oral Antidiabetic

Based on **Table 2** potential drug interactions in the oral antidiabetic type of 10.759 drugs (91.45%). Potential interaction occurred in the biguanide class, namely Metformin by 36.76% followed by sulfonylureas, glimepiride by 32.99%. Metformin, as a first-line monotherapy and as the most commonly prescribed drug turns out to also be the type of drug that most often potentially undergoes drug interactions. This is in line with a 2013 study that found that metformin is among the most interacting types of drugs, among the types of drugs that experience potential drug interactions, metformin ranks first. Metformin is a cationic drug that can interact with other cationic drugs through organic cationic ion transporters in the kidneys. Cationic drugs such as digoxin, trimethoptim, vancomycin, and cimetidine may interact with metformin in elimination in the kidneys, but only with cimetidine that causes lactic acidosis.

Table 2. Results of Analysis Potential Interactions Oral Antidiabetic

Drug Group	Total Number of Antidiabetic Drugs (n = 11.764)	
	Interact	Not Interacting
Biguanida:		
- Metformin	4.325(36,76%)	790(6,72%)
Sulfonylureas:		
- Glimepirid	3.882(32,99%)	100(0,85%)
- Glikazid	140(1,19%)	57(0,48%)
- Gliquidone	98(0,83%)	6(0,05%)
Thiazolidinedione:		
- Pioglitazone	2.004(17,04%)	45(0,38%)
Alpha-Glucosidase Inhibitor:		
- Akarbose	310(2,64%)	7(0,06%)
	10.759(91,45%)	**1.005(8,55%)**

Metformin is a recommended first-line therapy because it is proven to be effective, safe, inexpensive, and can lower the risk of cardiovascular events in patients with type 2 diabetes mellitus. In addition, metformin also has many benefits in therapy related to HbA1C levels, weight gain, and death due to cardiovascular events [6].

3.1.3 Incidence of Potential Oral Antidiabetic Interactions Based on Drug Interaction Mechanism Patterns And Severity of Drug Interactions

Based on **Table 3** types of potential oral antidiabetic interactions occurrences as many as 43 types.

Table 3. Types of Potential Oral Antidiabetic Interactions Based on Drug Interaction Mechanism Patterns And Severity of Drug Interactions.

No.	Drug Name		Drug Interaction Mechanism Patterns	Severity of Drug Interactions	Number of Cases
	Drug A	Drug B			
1	Akarbose	Warfarin	*Unknown*	*Minor*	96
2	Akarbose	Dexamethasone	Pharmacodynamics	*Moderate*	140
3	Akarbose	Levofloxacine	Pharmacodynamics	*Moderate*	74
4	Glimepirid	Omeprazole	Pharmacodynamics	*Minor*	35
5	Glimepirid	Methylprednisolone	Pharmacodynamics	*Moderate*	30
6	Glimepirid	Salbutamol	Pharmacodynamics	*Moderate*	15
7	Glimepirid	Ketorolac	*Unknown*	*Moderate*	36
8	Glimepirid	Metformin	Pharmacodynamics	*Moderate*	2.842
9	Glimepirid	Clopidogrel	Pharmacodynamics	*Minor*	24
10	Glimepirid	Moxifloxacin	Pharmacodynamics	*Major*	30
11	Glimepirid	Sucralfat	Pharmacokinetics	*Moderate*	90
12	Glimepirid	Rifampicin	Pharmacokinetics	*Moderate*	50
13	Glimepirid	Isoniazid	Unknown	*Moderate*	13
14	Glimepirid	Phenophans	Pharmacodynamics	*Moderate*	52
15	Glimepirid	Risperidon	*Unknown*	*Moderate*	78
16	Glimepirid	Clozapin	*Unknown*	*Moderate*	66
17	Glimepirid	Mefenamic Acid	*Unknown*	*Moderate*	101
18	Gliklazid	Levofloxacin	Pharmacodynamics	*Major*	140
19	Glimepirid	Ibuprofen	*Unknown*	*Moderate*	74
20	Glimepirid	Ranitidin	Pharmacokinetics	*Moderate*	26
21	Glimepirid	Antacids	Pharmacokinetics	*Moderate*	59
22	Glimepirid	aspirin	Pharmacodynamics	*Moderate*	93
23	Glimepirid	Hydrochlortiazid	Pharmacodynamics	*Moderate*	62

24	Glimepirid	Furosemid	*Unknown*	*Moderate*	69
25	Gliquidon	Captopril	Pharmacodynamics	*Moderate*	98
26	Glimepirid	Bisoprolol	*Unknown*	*Moderate*	37
27	Metformin	Ibuprofen	*Unknown*	*Moderate*	90
28	Metformin	Ketorolac	*Unknown*	*Moderate*	40
29	Metformin	Levofloxacin	Pharmacodynamics	*Moderate*	56
30	Metformin	Spironolakton	Pharmacodynamics	*Moderate*	118
31	Metformin	Dexamethasone	Pharmacodynamics	*Moderate*	192
32	Metformin	Ciprofloxacin	Pharmacodynamics	*Moderate*	149
33	Metformin	Moxifloxacin	Pharmacodynamics	*Moderate*	188
34	Metformin	Sucralfat	Pharmacokinetics	*Moderate*	167
35	Metformin	Meloxicam	Pharmacodynamics	*Moderate*	727
36	Metformin	Mefenamic Acid	Pharmacodynamics	*Moderate*	812
37	Metformin	Nifedipin	Pharmacokinetics	*Moderate*	134
38	Metformin	Ranitidin	Pharmacokinetics	*Moderate*	1.179
39	Metformin	Captopril	*Unknown*	*Moderate*	268
40	Metformin	Furosemid	*Unknown*	*Moderate*	205
41	Pioglitazone	Levofloxacin	Pharmacodynamics	*Moderate*	798
42	Pioglitazone	Salbutamol	Pharmacodynamics	*Moderate*	693
43	Pioglitazone	Isoniazid	Pharmacodynamics	*Minor*	513
	Total			**10.759**	

Based on **Table 3** it was obtained that the most interacting pairs were Glimepirid – Metformin (2.842 cases), Metformin – Ranitidine (1.179 cases), Metformin – Mefenamic Acid (812 cases). This result is no different from the research conducted by Mega Gustiani Utami 2013 which obtained a type of oral antidiabetic that often interacts is glimepiride and metformin. Biguanides and sulfonylureas affect the sensitivity of insulin receptors, so the combination of the two has a mutually supportive effect, where sulfonylureas will initiate by stimulating pancreatic secretions that provide opportunities for biguanide compounds to work effectively, experience shows that the combination of these two classes can be effective in many diabetics who were previously unhelpful when used alone.

Table 4. Types of Drug Interaction Mechanisms and Severity of Drug Interactions

No.	Mechanism of Drug Interactions	Number of Cases	%
1	Pharmacodynamic Interactions	7.881	73,25
2	Pharmacokinetic Interactions	1.705	15,85
3	*Unknown Interactions*	1.173	10,9
	Total	**10.759**	**100**
No.	**Severity**		
1	Minor	668	6,21
2	Moderate	9.921	92,21
3	Major	170	1,58
	Total	**10.759**	**100**

Based on **Table 4**, it was obtained that the most drug interaction mechanism is pharmacodynamic by 73.25%. This shows that the potential for more interactions occurs at the same level of the receptor system, physiological system, or workplace resulting in additive, synergistic and antagonistic effects [7]. The incidence of pharmacodynamic interactions can be foreseen so that it can be avoided in advance if known mechanisms of action of the drug [8].

Based on **Table 4** obtained the severity of drug interactions that occur the most is moderate by 92.21%. The most potential occurrence of moderate category interactions is glimepiride – metformin is known to have a

hypoglycemic effect, management for this potential interaction is the administration of low doses of glimepiride is required when administered simultaneously with metformin. Blood glucose should be monitored periodically and patients should be given education regarding hypoglycemic signs such as dizziness, headache, drowsiness, nervousness, confusion, tremor, hunger, weakness, palpitations, tachycardia [9][10].

IV. CONCLUSION

Based on the results of research can be concluded that an analysis of 9.818 prescription sheets of patients with type 2 diabetes mellitus, there were found 6.454 (65.73%) prescriptions to potential oral antidiabetic interactions.

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