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RESEARCH ARTICLE

Study of potential interactions of oral antidiabetic drugs in patients with type 2 diabetes mellitus with comorbidities: A retrospective study

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Abstract

Background: Diabetes mellitus (DM) has many complications, such as microvascular and macrovascular complications. Patients are given polypharmacy therapy to combat these issues, which can cause drug interactions. Oral antidiabetic drugs were chosen based on their risk profile. Risk assessment aided treatment intensity targeting. The number of drugs taken can increase the risk of drug interactions causing health issues. **Objective**: To identify potential drug interactions based on their severity (major, moderate and minor) and the mechanism of the drug interaction (pharmacokinetics and pharmacodynamics), in type two diabetes mellitus patients with comorbidities at the Lamongan Health Center. **Methods**: This was a cross-sectional study using medical records and patient prescriptions from October 2020 to June 2021 at *Puskesmas* (Primary Health Centers) Deket, Karanggeneng, and Babat. The data were descriptively analysed. Drug interactions were analysed using drugs.com and Stockley. Purposive sampling was used to select 194 patients for inclusion. **Results**: From October 2020 to June 2021, 110 out of 194 outpatients at Lamongan Regional Health Center had potential drug interactions (56.7 %). The most common type of drug interaction was of moderate severity, with 120 cases (93.0%), and the most common mechanism was pharmacodynamics (61.2%). **Conclusion**: Polypharmacy is a difficult problem to avoid, so drug therapy monitoring is required in diabetic patients to minimise unwanted effects. Preventing potential drug interactions requires a system for early detection of potential drug interactions that may occur in patient prescribing and maximising pharmaceutical care. This system would allow for the community to be more proactive in finding out about potential drug interactions.

Introduction

Type 2 diabetes (T2D) is a tremendously regular, multisystemic, chronic metabolic disorder associated with atherosclerosis and cardiovascular disease. It is characterised by mitochondrial dysfunction and the presence of oxidative stress. The risk of diabetes mellitus (DM) is frequently considered equivalent to the risk of cardiovascular disease (CVD); however, the variation in CVD risk in adults with DM has not been elucidated (Wong *et al.,* 2012). DM has become a global epidemic and causes many complications, usually proportional to the degree and duration of hyperglycemia (Mauri-Obradors *et al.*, 2017). Epidemiological and clinical data from the last two decades show that the prevalence of heart failure in diabetes is very high, and the prognosis for patients with heart failure is worse in those with diabetes than in those without diabetes (Lehrke & Marx, 2017).

Worldwide, drug interactions still cause significant preventable therapy failures. Over a 20-year period, the WHO Global Individual Case Safety Report database discovered 3766 drug interaction cases. Metformin and amlodipine were the most likely drugs to interact. This interaction was found in 53 cases, according to other researchers (50.47 %). With the highest level of interaction severity, hypoglycemia becomes a concern (Sukmaningsih, 2021). Hypoglycemia is a dangerous condition that can occur due to undetected drug

interactions. Hypoglycemia occurs when the patient's blood sugar falls below normal. A tingling or numb feeling in the lips or tongue can be a sign of this condition. Preventing this interaction requires a time lag between doses. The risk of moderate drug interactions increases with age, physiological conditions of the body, and increased risk of chronic disease and its complications, which causes the patient to take more than one drug (Chawla *et al.,* 2016).

It is essential for potential drug-drug interactions to be identified in pharmaceutical services. Geografi dan Simbolon (2020) discovered that the use of antihyperglycemic drugs concurrently with antihypertensives had the potential to cause 16 types of drug interactions (23%) in a total of 30 events. The safety profile of a drug is only obtained after extensive community distribution, including patients who were not previously represented in clinical trials, such as diabetes mellitus patients with comorbidities receiving high doses of the drug. Polypharmacy is directly related to drug interactions. The high number and variety of drugs taken by DM patients put them at risk for drug interactions. Comorbidities in DM patients necessitates medication because, in addition to treating major ailments, comorbidities can worsen hypertension or accelerate and worsen health. The high number of potential drug interactions in this study is linked to comorbidities and the number of drugs prescribed to the patient. As a result, it can take months or even years to collect adequate data on drug interactions.

To identify potential drug interactions in diabetic patients with comorbidities or complications, a study is required. This study's goal is to identify drug interactions in patients with type 2 diabetes at Lamongan's Puskesmas.

Methods

This study is non-experimental survey research employing a descriptive survey method. Data collection techniques were performed retrospectively in three Puskesmas located in the Lamongan area, which were Kranggeneng, Babat and Lamongan Health Centers. Data were obtained from the medical records and prescriptions for patients diagnosed with type 2 diabetes mellitus with comorbidities in the period of October 2020 - June 2021 who met the inclusion criteria. The inclusion criteria of this study were outpatients diagnosed with diabetes mellitus with certain comorbidities (cardiovascular, respiratory, infectious, bone and joint disease), adult patients aged ≥ 18 years, medical record sheets and written prescriptions in full. The data obtained then identified potential drug interactions based on the mechanism of drug interaction (pharmacodynamics, pharmacokinetics) and severity (minor, moderate, major) using the drugs.com application and Stockley literature. Furthermore, the data was tabulated, and conclusions were implied.

Results

The number of outpatients in type 2 diabetes mellitus patients with comorbidities in *Puskesmas* Lamongan in the period of October 2020 - June 2021 totalled 194 patients. This research was done by collecting data through prescriptions and patient medical records. Based on the research results obtained in Table I, the study reveals that the highest number of patients (101 patients; 52.06%) with type 2 DM disease were aged between 56 - 65 years. In DM patients, other comorbid diseases followed, such as hypertension (158 patients). After that, identified in Table II, in this study, most of the potential drug interactions occurred in 110 patients (56.70%).

Table I: Characteristics of diabetes mellitus patients with comorbidities

Characteristics	Total	Percentage (%)
Gender		
Male	76	39.18
Female	118	60.82
Age (years)		
36 - 45	3	1.55
46 - 55	20	10.31
56 - 65	101	52.06
>65	70	36.08
BMT (kg/m^2)		18.04
Normal (18,5-22,9)	35	31.96
Overweight (23,0-24,9)	62	50.00
Obese (≥25,0)	97	73.71
Comorbidities		9.28
Hypertension	158	11.34
Coronary heart disease	11	1.03
Dyslipidemia	9	0.52
Tuberculosis	7	3.09
Chronic obstructive pulmonary disease	1	1.03
Osteoarthritis	6	39.18
Gout	2	60.82
Total	**194**	**100**

Table II: Incidence of drug interactions

Incidence of interactions	Total patients	Percentage (%)
With potential drug interactions	110	56.70
Without potential drug interactions	84	43.30
Total	**194**	**100**

Based on Table III, glimepiride is a sulfonylurea group that is widely prescribed (15.96%). The results of this study also revealed that hypertension was the most general comorbidity in type 2 DM patients, with the most used antihypertensive drugs being the CCB (Ca Channel Blocker) group, amlodipine. Antihyperglycemics with antihypertensives were most common in the use of glimepiride with bisoprolol (13%) and insulin with bisoprolol (13%).

Table III: Types of prescribed drugs

Drug class	Drug type	Total patients[†]	%
Sulfonylurea	Glimepiride	64	15.96
	Glibenclamide	37	9.23
Biguanida	Metformin	51	12.72
Calcium Channel Blocker	Amlodipine	57	14.21
B-Blocker	Bisoprolol	10	2.49
ACEI	Captopril	14	3.49
	Lisinopril	2	0.50
ARB	Candesartan	1	0.25
Loop Diuretic	Furosemide	12	2.99
NSAID	Sodium Diclofenac	33	8.23
	Mefenamic acid	9	2.24
	Ibuprofen	5	1.25
	Piroxicam	4	1.00
Corticosteroid	Dexamethasone	1	0.25
	Methylprednisolone	1	0.25
Antibiotic	Rifampicin	7	1.75
Xanthine-oxidase	Allopurinol	2	0.50
Antacid	Aluminium Hidroksida+Magnesium Hidroksida	6	1.50
Nitrate	Isosorbide dinitrate	5	1.25
H2 Antagonist	Ranitidin	8	2.00
PPI	Omeprazole	2	0.50
COX Inhibitor	Salicylic acid	6	1.50
Statin	Simvastatin	8	2.00
Penicillin antibiotic	Amoxicillin	2	0.50
Antihistamine 2nd generation	Cetirizine	5	1.25
Antipyretics	Paracetamol	5	1.25
Antidiarrheal	Attapulgit	2	0.50
Antivertigo	Betahistin	1	0.25
Antiemetic	Domperidone	1	0.25
Mucolytic	Ambroxol	2	0.50
Vitamin	Vitamin B1+B6+B12	37	9.23
Fibrate	Gemfibrozil	1	0.25
Total		**401**	**100**

[†]1 patient gets more than one type of therapy in the prescription sheet; ACEI - Angiotensin-converting enzyme inhibitors; ARB – Angiotensin receptor blockers

Discussion

It is in accordance with data in the journal (Singh *et al.*, 2014) that ages > 55 years are at risk of developing type 2 DM because of degenerative factors. These factors were decreased body function and glucose intolerance which causes a lack of pancreatic beta cells producing insulin. This makes body fat distribution easy to accumulate postmenopause; hence, women tend to possess an increased body mass index, as presented in Table I. The majority of respondents with type 2 diabetes were obese with a BMI value ≥ 25.0 kg/m^2 (97 patients; 73.71 %). Obesity is one of the factors influencing the onset of type 2 DM because excessive lipid deposits in the body affect sugar levels and cause cells to become insensitive to insulin (insulin resistance) (Simbolon *et al.,* 2020).

In research by Tsimihodimos and colleagues (2018), it is stated that there is a close relationship between DM patients and hypertension. It is due to the disruption of carbohydrate metabolism in DM patients that results in an increase in triglycerides, affecting the plaque occurrence and eventually triggering an increase in blood pressure. Therefore, it is necessary to consider the incidence of interactions between drugs that potentially occurs.

The most broadly administered drugs in therapy are sulfonylureas, which are more effective in reducing blood sugar levels in patients whose pancreatic-cell function produces insulin. Glimepiride possesses fewer adverse hypoglycemic effects than glibenclamide. As seen in a study by Tornio and colleagues (2012), for geriatric patients, the administration of glibenclamide is not recommended because it has a 52% higher chance of causing hypoglycemia compared to other sulfonylurea groups. Thus, it is preferred to provide glimepiride to the geriatric patients that dominate the results of this study. Furthermore, the use of monotherapy with other oral antidiabetics, such as metformin, can be the first choice of therapy for the treatment of type 2 diabetes mellitus. It also helps with weight loss for obese patients. If, after performing monotherapy for three months, blood glucose levels do not acquire the target, it is recommended to conduct a combination of oral antidiabetic drugs, such as the results of this study which provided a combination of glimepiride and metformin (Saldanha De Mattos Matheus & Brito Gomes, 2013).

Combination therapy is more effective in controlling hyperglycemia and possesses minimum adverse effects compared to monotherapy in patients with uncontrolled blood glucose. The combination of glimepiride with metformin was more efficient in controlling HbA1c, fasting blood glucose, and postprandial blood glucose. Amlodipine is recommended for diabetic patients with hypertension because CCBs do not affect insulin sensitivity or glucose metabolism. Moreover, amlodipine has also been displayed to be more effective at lowering blood pressure. It is also well absorbed and causes less adverse vasodilation effects than other CCB groups in geriatric patients (Lee *et al.,* 2014). As there is a presence of comorbid hypertension and other types of comorbidities in diabetic patients, the potential for problems associated with drugs *(*Drug Related Problems), which are drug interactions, should be considered.

The combination of glimepiride and bisoprolol has the potential for pharmacodynamic interactions because beta-blockers can inhibit some of the normal physiological responses to hypoglycemia, such as tachycardia, tremors and shaking. The catecholamine-mediated inhibition of glycogenolysis and glucose mobilisation in conjunction with beta-receptor inhibition may potentiate insulin-induced hypoglycemia in diabetics and delay the restoration of normal blood glucose levels. Other effects reported with various beta-blockers include decreased glucose tolerance and decreased glucose-induced insulin secretion.

Table IV demonstrates that the mechanism of potential drug interactions that dominates this study is pharmacodynamic (72.41%). It indicates that the effect of one drug is altered by another drug at its site of action. For example, the interaction between metformin and glimepiride is of moderate severity. The combination of metformin and glimepiride simultaneously is effective in improving glycemic control and can provide a weight loss effect, especially in obese patients, as seen in the results of this study. In a study by Laakso (2011), the use of a combination of metformin and glimepiride was proven to have a lower risk of hypoglycemic side effects compared to the combination of metformin and glibenclamide. Likewise, in a double-blind study, glimepiride was significantly less hypoglycemic (1.7%) than glibenclamide (5.6%). Symptoms of hypoglycemia include headache, dizziness, drowsiness, nervousness, tremors, and a fast heart rate. In order for these two drugs to be used safely, it is necessary to monitor blood sugar on an ongoing basis.

Table IV: Types of drug interactions by mechanism and severity

Mechanism	Drug A	Drug B	Severity	Total patients	Percentage (%)
Pharmacodynamic (n = 21 cases)	Glibenclamide	Metformin	Moderate	1	0.81
		Captopril	Moderate	4	3.25
		Bisoprolol	Moderate	4	3.25
		Na.Diclofenac	Moderate	1	0.81
		Methylprednisolone	Minor	1	0.81
	Metformin	Na.Diclofenac	Moderate	15	12.20
		Glimepiride	Moderate	16	13.01
		Captopril	Moderate	5	4.07
		Lisinopril	Moderate	1	0.81
		Mefenamic acid	Moderate	4	3.25
		Ranitidine	Moderate	2	1.63
		Furosemide	Minor	5	4.07
	Glimepiride	Captopril	Moderate	5	4.07
		Lisinopril	Moderate	1	0.81
		Mefenamic acid	Moderate	3	2.44
		Ibuprofen	Moderate	3	2.44
		Na.Diclofenac	Moderate	16	13.01
		Ranitidine	Moderate	3	2.44
		Bisoprolol	Moderate	5	4.07
		Dexametasone	Minor	1	0.81
		Furosemide	Minor	2	1.63
Pharmacokinetic (n = 8 cases)	Glibenclamide	Rifampicin	Moderate	6	4.88
		Ibuprofen	Moderate	2	1.63
		Mefenamic acid	Moderate	2	1.63
		Ranitidine	Moderate	3	2.44
	Metformin	Rifampicin	Moderate	1	0.81
	Glimepiride	Antasida	Moderate	6	4.88
		Gemfibrozil	Moderate	1	0.81
		Piroxicam	Moderate	4	3.25

Another oral antidiabetic (OAD) interaction is metformin with NSAIDs (Non-Steroid Anti-Inflammatory Drugs) and diclofenac sodium. NSAIDs reduce the effectiveness of oral antidiabetics. NSAIDs work by inhibiting the antidiabetic effect. To reduce the incidence of interactions between the two drugs, there must be dose adjustment and evaluation of blood glucose control (May & Schindler, 2016). An example of pharmacodynamic interactions is the interaction between glimepiride and ACE inhibitors. The ACE inhibitor, captopril, increases insulin sensitivity. Captopril increases bradykinin production but reduces glucose production by the liver. Hypoglycemia was discovered as an adverse effect of captopril. The concomitant use of these two drugs causes an agonist effect, which is the stimulation of insulin secretion that then causes an increase in hypoglycemia (Baxter, 2010).

Other pharmacodynamic interaction mechanisms, such as metformin and ranitidine, possess the potential to increase the effect of metformin by decreasing renal clearance, which inhibits the secretion of metformin in the kidney tubular; thus, metformin plasma levels increase and escalate its pharmacological effects. Therefore, it is recommended to change therapy. Using metformin together with ranitidine can potentially cause lactic acidosis (Tornio *et al.,* 2012).

The potential for severe pharmacokinetic interactions is perceived through the interaction between piroxicam and glimepiride. The combination of the two drugs potentially increases the effects of glimepiride and causes blood sugar levels to become too low. Piroxicam

is an inhibitor of the CYP2C9 enzyme, while glimepiride in the body is metabolised by the CYP2C9 enzyme. Piroxicam acts as an inhibitor of the CYP2C9 enzyme and inhibits glimepiride metabolism. Thus, it increases the glimepiride concentration in the body and causes a hypoglycemic effect. Piroxicam is a class of NSAID drugs that increases the action of glimepiride by increasing insulin release through the inhibition mechanism of potassium ion channels in pancreatic beta cells (Baxter, 2010).

Based on the level of severity, the results revealed that apart from moderate severity, there was also a minor level of severity. The potential for drug interactions with minor severity possesses a mild effect or may not occur and won't affect the outcome of therapy; thus, it does not require additional therapy (Meryta *et al.,* 2017). Drug interactions with minor severity have little effect on the therapeutic response of the drug, the clinical impact is less significant, and it is not necessary to change the therapeutic regimen, such as with the interaction of glimepiride with dexamethasone.

Conclusion

Problems associated with polypharmacy are difficult to avoid. Drug therapy for patients with diabetes mellitus needs to be monitored so that the possibility of unwanted effects can be minimised based on the mechanisms of pharmacodynamic interactions (72.4%). When drug interactions were classified based on the severity, the most common was moderate severity (86.2%). Pharmacists should evaluate potential drug interactions that can occur in patients when prescribing and maximising pharmaceutical care in order to prevent potential drug interactions. This will allow there to be a system for early detection of potential drug interactions that may happen and endanger the patient. The community must be more proactive in finding out information about potential drug interactions that may happen when taking different types of drugs at the same time.

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