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Identification of Adverse Drug Reactions of Antidiabetic Drugs Among Hospitalized Elderly Patient with Diabetes

Aida Udhiyati[1], Fita Rahmawati[2*]
[1] Master of Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
[2] Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Gadjah Mada
Corresponding author: Fita Rahmawati; Email: rahmawati_f@ugm.ac.id
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ABSTRACT

The pharmacologic management of many acute and chronic conditions and the aging population have contributed to increasing medication use among elderly patients, this situation may lead to drug-related problems (DRPs) especially adverse drug reactions (ADR). This study aims to identify ADR of antidiabetic drugs among hospitalized elderly patient with diabetes. This descriptive observational study with a cross sectional design involved 98 geriatric patients at UGM Academic Hospital that admission between January to December 2021. The inclusion criteria were patients aged above 60 years, has complete medical record and patient was diagnosed with diabetes. WHO-UMC causality assessment criteria and Hartwig and Siegel's scale was used for the assessment of causality and severity of ADRs, respectively. Number of patients who had experienced ADR were 15 (15.31%) patients with total ADR event were 15 (15.31%) ADRs. The result recorded 11 (11.22%) patients experienced ADR with causality category *possible* and severity category *moderate*, and 4 (4.09%) patients experienced ADR with causality category *possible* and severity category *mild*. Clinical manifestation of those ADR were nausea, heartburn, hypokalemia and hypoglycemia. The suspected antidiabetic drugs that caused ADR were metformin and insulin. Given pharmaceutical care among elderly with diabetes is pivotal to prevent ADR of antidiabetic drugs.
Keywords: antidiabetic drugs; adverse drug reaction; elderly; diabetes

INTRODUCTION

The results of World Health Organization (WHO) evaluation show that in every nine people there is one elderly person (60 years old or older). By 2050, the value is expected to increase to one in five people (Dagli and Sharma, 2014). In Indonesia, The predicted number of the elderly population in 2020 is 27,08 million, in 2025 is 33,69 million, in 2030 is 40,95 million and in 2035 is 48,19 million (Pusdatin, 2017).

The demographic transition in the elderly population constitutes a significant challenge for health authorities worldwide as with advancing age multiple chronic diseases such as hypertension, diabetes mellitus, arthritis, chronic heart disease, renal diseases, etc. are associated. As a result of which elderly people tend to take multiple medications in a day that can be referred to as polypharmacy, thus increasing ADR risk through drug–drug and drug–disease interactions (Dagli and Sharma, 2014).

Indonesian Basic Health Research Results in 2018 showed that diabetes is included in the top five incommunicable diseases. In 2019, it was estimated that 19.3% of people aged 65-99 years (135.6 million people) live with diabetes. The results of Dobrică *et al* (2019) study showed that patient with type 2 diabetes mellitus has more comorbidities and receive more drugs compared to non-diabetes patients. The average prescribed drugs for type 2 diabetes mellitus patients and non-diabetes patients were 7.81 ± 2.23 and 5.33 ± 2.63, respectively.

ADRs were associated with a significantly prolonged length of hospital stay for adult medical inpatients (Fasipe *et al*., 2019). Out of 61,661 patients, there were 2491 patients (4%) experienced 3144 ADR (Sato and Akazawa, 2013). The increase in the prevalence of diabetes cases and elderly highlights the need for clinical pharmacists to identify the ADR of anti-diabetic drugs.

This study aims to identify the ADR of antidiabetic drugs among hospitalized elderly patients with diabetes. The result can show us the importance of ADR identification so that pharmacist can preventing ADR to occurs.

METHODS

This was a descriptive observational study with a cross sectional design. The ethical clearance was obtained from Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Gadjah Mada University. The data was collected from UGM Academic Hospital medical record from patient admission January to December 2021.

Subjects for this research were the patients which met the inclusion criteria. The inclusion criteria of the study were hospitalized patients aged more than 60 years, patients with DM, receive anti diabetic drug and had complete medical records. The exclusion criteria included cancer patients receiving chemotherapy and patients receiving systemic immunosuppressant therapy.

The research sample size was obtained by using the population formula to determine the following proportions (Lemeshow *et al*., 1990):

$$n = \frac{Z_{\alpha/2}{}^2 P(1-P)}{d^2}$$

Based on the calculation above with confidence level 95% (α=5%), The value of P is 0.2. It was obtained from ADR proportions of elderly hospitalized patient with DM. And d value (absolute precision required) is 0.10. The calculated minimal sample size is 62. The sample size for this study was 98 and had met the minimum sample size. Sampling technique for this study was using purposive sampling.

Identification of ADR was carried out by collecting patient's drug use, clinical condition, vital signs, laboratory data and others examination, follow by study literature was conducted to identify the suspected drug. WHO-UMC causality assessment criteria and Hartwig and Siegel's scale was used for the assessment of causality and severity of ADRs, respectively. WHO-UMC Causality assessment categorize causality into six category ("certain", "probable/likely", "possible", "unlikely", "conditional/unclassified", and "unassessable/unclassifiable") according to event or laboratory data abnormality, onset of ADR, withdrawal information and disease or other drugs that may contribute to ADR. Hartwig and Siegel's scale categorize ADR severity into seven levels and three grade according to clinical consequence, including resultant harm and intensity of medical intervention required. Those three grades are mild (levels 1 and 2), moderate (levels 3 and 4), and severe (levels 4,5, and 7).

Causality assessment was conducted by two pharmacists. The subject characteristics, causality and severity of ADR was presented in the table descriptively and served as frequency and percentage.

RESULT AND DISCUSSION

The characteristic of the research was obtained through descriptive analysis. The characteristic of the study include: sex, age, and comorbidity (non-diabetic).

The patient characteristics on Table I showed that the prevalence of elderly patients in males and females was almost similar with female prevalence slightly higher. This data was similar to the results from study conducted by Jain (Jain and Paranjape, 2013) and Rathmann(Rathmann *et al*., 2005). Another study showed that the prevalence of type 2 diabetes mellitus was higher in males (Nordström *et al*., 2016). Those differences may be resulted from the different number of males or females being included in the study.

The distribution data of hospitalized elderly patient with diabetes was highest in category 60-74 years old, followed by category >75-84 years old, and the lowest in category > 85 years old. Those results was similar with National Report of Basic Health Research in 2018 (Kementerian Kesehatan RI, 2019). The report showed that the prevalence of diabetic patients was higher in age groups 55-64 years old and 65-74 years old compared to age group > 75 years old.

Elderly people with diabetes have significantly more comorbidities compared to those without diabetes (Schernthaner and Schernthaner-Reiter, 2018). ADR was found more frequent in patients with comorbidity (66,2%) compared to patients without comorbidity (Bassi *et al*., 2017). Renal disease is the most comorbidity patient has with percentage 41.44%, followed by cerebrovascular disease, congestive heart failure, ulcer, myocardial infarction, and chronic pulmonary disease with percentage 23.42%, 19.82%, 9.01%, 5.41% and 0.90%, respectively.

Table I. Characteristics of Hospitalized Elderly Patient with Diabetes at UGM Academic Hospital Yogyakarta January – December 2021

Characteristics	Subjects (n=98)	Percentage
Sex		
Male	41	41.84%
Female	57	58.84%
Age (years old)		
60 – 74	79	80.62%
≥ 75-84	18	18.37%
≥ 85	1	1.02%
Comorbidity		
Myocardial infarction	6	5.41%
Renal disease	46	41.44%
Cerebrovascular disease	26	23.42%
Congestive Heart Failure	22	19.82%
Ulcer	10	9.01%
Chronic Pulmonary Disease	1	0.90%

Note: one patient may have more than 1 comorbidity

Table II showed that the most antidiabetic drug prescribed was insulin rapid acting (30.61%), followed by metformin (10.20%). The most used combination of antidiabetic drugs was insulin glargine and insulin rapid acting (9.18%). It had similar result from another study showed that metformin was the most used antidiabetic drug (Putra *et al*., 2017).

Table III summarized that there were 15 ADR events encountered and total 15 patients had experienced ADR. According to Table III, it was found that the most frequent ADR was hypokalemia due to insulin rapid acting or insulin long-acting administration.

Hypokalemia is defined as a plasmatic potassium (K^+) concentration < 3.5 mEq/L. Mild hypokalemia is a serum level of 3.0–3.4 mEq/L, moderate hypokalemia is a serum level 2.5-2.9 mEq/L), and severe hypokalemia is a serum level of <2.5 mEq/L (Kardalas *et al*., 2018). In this study, 6 patients who had experienced hypokalemia, categorized as mild hypokalemia, while others 5 patients categorized as moderate hypokalemia.

The prevalence of hypokalemia in individuals over 55 years of age and with diabetes, varies between 1.0 and 1.2%. This prevalence is even higher in individuals with associated CKD and increased with age (Jiménez-Marrero *et al*., 2020). One of the medications that contributes to hypokalemia in individuals with diabetes is insulin (Coregliano-Ring *et al*., 2022). High dose of insulin can lead to hypokalemia (Muneer and Akbar, 2021), which is the most common cause of low serum K^+ concentrations in individuals with DM (Gennari, 1998). The physiological response to insulin is the activation of the sodium-potassium ATPase (Na^+-K^+-ATPase) pump, promoting the rapid entry of K^+ into peripheral cells. In addition, the insulin-induced passage of glucose into cells is a fuel source to maintain the action of the Na^+-K^+-ATPase pump, providing feedback for this K Na^+-K^+-ATPase transport mechanism (Coregliano-Ring *et al*., 2022).

Nausea was encountered on one patient who receive metformin (1.02%). Nausea, vomiting, diarrhea, and heartburn are quite common gastrointestinal side effects of metformin (Ashraf *et al*., 2022). Gastrointestinal (GI) adverse events (AEs) of metformin that typically encountered are diarrhea, nausea, flatulence, indigestion, vomiting, and abdominal discomfort (Bonnet and Scheen, 2017). Nausea is the second common symptom after diarrhea (Turner *et al*., 1998). The underlying mechanism of metformin-associated GI intolerance are poorly known. The gut may be responsible for some of metformin's GI intolerance by exerting effects on gut microbiota flora, increasing intestinal glucose turnover, and increasing the concentration of glucagon-like peptide 1 (Bonnet and Scheen, 2017). The composition and function of gut bacteria were recently shown due to metformin, potentially explaining both some of metformin's beneficial and GI AEs (Forslund *et al*., 2015).

Table II. Percentage of antidiabetic drugs that prescribed to Hospitalized Elderly Patient with Diabetes at UGM Academic Hospital Yogyakarta January – December 2021

Antidiabetic Drug Use and Drug Class	Drug name	Number of patient (n= 98)	Percentage
Monotherapy			
Biguanide	Metformin	10	10.20%
Sulfonylurea	Gliquidone	2	2.04%
	Glimepiride	2	2.04%
TZD*	Pioglitazone	2	2.04%
Insulin rapid acting	Insulin rapid acting	30	30.61%
Insulin intermediate acting	Insulin intermediate acting	6	6.12%
Insulin long acting	Insulin Glargine	6	6.12%
Combination of 2 drugs			
Biguanide + sulfonylurea	Metformin + gliquidone	1	1.02%
	Metformin + glimepiride	6	6.12%
	Metformin + gliclazide	1	1.02%
Biguanide + TZD*	Metformin pioglitazone	1	1.02%
Biguanide + AGi*	Metformin + acarbose	2	2.04%
Sulfonylurea + AGi*	Glimepiride + acarbose	1	1.02%
Biguanide + insulin rapid acting	Metformin + insulin rapid acting	5	5.10%
Biguanide + insulin long acting	Metformin + insulin glargine	1	1.02%
Insulin rapid acting + sulfonylurea	Insulin rapid acting + gliquidone	2	2.04%
Insulin long acting + sulfonylurea	Insulin glargine + gliquidone	1	1.02%
Insulin rapid acting + insulin intermediate acting	Insulin rapid acting + insulin intermediate acting	1	1.02%
Insulin long acting + insulin rapid acting	Insulin glargine + insulin rapid acting	9	9.18%
Insulin long acting + insulin intermediate acting	Insulin glargine + insulin intermediate acting	1	1.02%
Combination of 3 drugs			
Biguanide + AGi* + insulin intermediate acting	Metformin + acarbose + insulin intermediate acting	1	1.02%
Biguanide + AGi* + insulin rapid acting	Metformin + acarbose + insulin rapid acting	1	1.02%
Biguanide + DPP-IV Inhibitors* + sulfonylurea	Metformin + vidagliptine + glimepiride	1	1.02%
Biguanide + DPP-IV Inhibitors* + TZD*	Metformin + vidagliptine + pioglitazone	1	1.02%
Biguanide + DPP-IV Inhibitors* + insulin long acting	Metformin + vidagliptine + insulin glargine	1	1.02%
Biguanide + insulin long acting + insulin rapid acting	Metformin + insulin glargine + insulin rapid acting	1	1.02%
TZD + insulin rapid acting + insulin long acting	Pioglitazone + insulin rapid acting + insulin glargine	1	1.02%
Combination of 4 drugs			
Insulin long acting + insulin rapid acting + TZD* + biguanide	Insulin glargine + insulin rapid acting + pioglitazone + metformin	1	1.02%

Note: *DPP-IV Inhibitors = Dipeptidyl peptidase IV Inhibitors; AGi = Alpha-glucosidase Inhibitors; TZD = Thiazolidinediones

Table III. The Number of ADR on Antidiabetic drug administration

Drug Name	ADR	Frequency	Percentage
Metformin	Nausea	1	1.02%
	Heartburn	1	1.02%
Insulin rapid acting	Hypokalemia	10	10.20%
	Hypoglycemia	2	2.02%
Insulin long acting	Hypokalemia	1	1.02%

Table IV. Causality and Severity Category of ADR due to Metformin

ADR	Causality Category	Severity Degree	Frequency
Heartburn	Possible	Moderate	1
Nausea	Possible	Moderate	1

Table V. Causality and Severity Category of ADR due to Insulin Rapid Acting

ADR	Causality Category	Severity Degree	Frequency
Hypokalemia	Possible	Moderate	7
	Possible	Mild	3
Hypoglycemia	Possible	Moderate	2

Table VI. Causality and Severity Category of ADR due to Insulin Long-acting

ADR	Causality Category	Severity Degree	Frequency
Hypokalemia	Possible	Moderate	1

Hypoglycemia was encountered in 2 patients after insulin rapid acting administration. A systematic review found that another factor that could have caused hypoglycemia, the most common of which was being on insulin or sulfonylureas (Murad *et al*., 2009).

In Table IV, metformin had caused heartburn and nausea. Heartburn might be caused by another concomitant drug like aspirin (Lacy *et al*., 2008), hence this ADR included as possible. Metformin discontinuation and lansoprazole administration made this ADR categorized as moderate. Nausea was encountered in one patient. This ADR included as possible category because nausea might be caused by other concomitant drugs patient took, like ceftriaxone, metronidazole and paracetamol (Lacy *et al*., 2008). According to severity analysis, it was included as moderate degree because ondansetron was administered to treat nausea.

All hypokalemia shown in Table V and Table VI categorized as possible because another concomitant drug that patient took, like furosemide, might contribute to this ADR (Lacy *et al*., 2008). There were 8 ADR events included as moderate degree because potassium supplementation was given to treat hypokalemia. Meanwhile, ADR that did not required treatment and no discontinuation of insulin categorized as mild degree.

In Table V, hypoglycemia was encountered in 2 patients. Hypoglycemia included as possible was not discontinued hence it made withdrawal information was unclear. It included as moderate category due to dextrose 40% administration to treat hypoglycemia. One patient who experienced hypoglycemia received combination of two antidiabetic drugs, insulin glargine and insulin rapid acting, while another patient only received insulin rapid acting.

This study had limitations. First, further causes of some ADRs could not be identified, for example cause of hypoglycemia due to insulin cannot be identified whether it was contributed by incorrect administration of insulin or not. This study could not identify ADR of antidiabetic drugs with small frequency because of limited sample.

CONCLUSION

In this study, it was reported that ADR of antidiabetic drugs in elderly patient was encountered in 15 (15.31%) patients. Pharmacist need to improve their role in preventing ADR of antidiabetic drugs to occur.

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