Original Article

Drug Related Problems (DRPs) Identification on Diabetes Melitus Type 2 Ward Patients with Complication

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Abstract

Management of Type 2 Diabetes Mellitus (DM) with long-term drug therapy may affect the patient's quality of life and may also lead to Drug Related Problems (DRPs) which may lead to less optimal treatment, increased side effects and costs treatment becomes expensive. This study aimed to determine the incidence of DRPs, the number of DRPs and the influence of the number of drugs on the incidence of DRPs that potentially affect the effectiveness of therapy in patients with type II DM in the ward patient Installation. This researches non experimental, observational with descriptive data analysis and retrospective data retrieval. The results obtained from 100 samples that met the inclusion criteria showed that the most prevalent DRPs category was drug interaction of 94.62%, then the above treatment dose was 2.93%, non-drug therapy or additional therapy required 1.46% , sub therapy dose 0,48% and drug without indication equal to 0,48% and there is influence between amount of drug usage to incidence DRPs proved with result of statistical analysis obtained probability value 0,002 (P <0,05).

Keywords: Type 2 Diabetes Mellitus , Drug Related Problems, Complication

INTRODUCTION

Diabetes mellitus (DM) is one of non-communicable diseases which its occurrence is increasing every year. In 2015, the number of DM patients was 415 million of adults and is expected to increase to 642 million by 2040. Indonesia is ranked seventh in the world with an estimated number 10 million of patients [1]. Hyperglycemia in DM patients can cause damage to organs, especially the nervous system and blood vessels. Macrovascular and microvascular complications often occur in DM patients such as hypertension, coronary heart disease and peripheral vascular disease [2].

DM treatment requires a long period of time especially if there are complications causing the amount of drugs consumed also increases. This polypharmacy (multiple drug therapy) which increases the incident of drug related problems (DRPs). The high incident of DRPs causes disruption of treatment which results in not achieving the therapeutic effect [3-4].

Research related to DRPs in Indonesia is still limited so more research is needed to find out whether the treatment given is rational, effective and safe for patients. The results of a study identifying, DRPs in type 2 DM patients with cirrhosis in Surabaya showed the highest percentage of DRPs was non-optimal drug therapy (54.9%) [4]. Whereas, the results of research on the identification of DRPs in type 2 DM patients in Jember showed that the highest DRP was drug interactions (66.67%) [5]. Another DRPs study in patients with type 2 DM and hypertension complications showed the highest incidence of DRPs was the inaccurate selection of combination drugs (71 patients) [6]. Therefore, this study was conducted as an effort to understand the potential and mechanisms regarding the occurrence of DRPs in type 2 DM patients in one of hospital in Indonesia.

METHODS

This research was conducted with a retrospective cross sectional design using medical records of type 2 DM patients hospitalized in Marzuki Mahdi Hospital, Bogor. This research conducted for two months from May to June 2018. The samples needed in this study were 100 samples with purposive sampling. Inclusion criteria in this study were patients diagnosed with type 2 DM with cardiovascular complications, aged> 40 years and using more than 3 kinds of drugs. Type 2 DM patients who were pregnant, postoperatively and treated <2 days were excluded from the study. This research has received ethical clearance from the Ethics Commission of Padjajaran University, Bandung. Data on age, sex, amount of drug use, dosage and frequency of drugs, duration of drug use, and laboratory results were taken from medical records that included inclusion criteria.

The collected data was analyzed for DRPs events using guidelines from PCNE Vol 6.2 2010. Analysis of the incident of DRPs was carried out using literature. The literature used is the American Standards of Medical Care in Diabetes 2018, Drug Interaction, Drug Information Handbook, and the Indonesian Endocrinology Society. Statistical analysis was used in this study to determine the effect of the amount of drug use on the incident of DRPs using Chi Square method with a confidence level of 95%.

RESULTS AND DISCUSSION

The samples included in the inclusion criteria of this study were 100 samples. From 100 samples, it can be seen that the number of women is more than 58% compared to men which is 42%. The most age is seen at age> 50 years which is 91%. In addition, most of the

complications of type 2 DM patients in this study were hypertension (31.96%), followed by Congestive Heart Failure (14.75%) and Chronic Kidney Disease (9.01%). Another characteristic analyzed is the amount of drug use. It can be seen that the highest number of drug uses is 6-10 drugs.

Table 1. Characteristic Patient of Type 2 Diabetes Mellitus With Complication (n = 100)

Characteristic	Percentage (%)
Gender	
Men	42
Women	58
Age	
< 50 years	9
>50 years	91
Macrovascular	
Hipertension	31.96
Congestive Heart Failure	14.75
Stroke	9
Hypertension Heart Disease	5.73
Unstable Angina Pectoris	4.09
Cerebrovascular disease	2.45
Cardiovascular disease	0.81
Non ST elevation myocard infarction (NSTEMI)	0.81
Microvascular	
Nefropathy diabetic	1.63
Acute Kidney Injury	1.63
Neuropathy	0.81
Chronic kidney disease	9.01
Non Cardiovascular	
Gastroenteritis	4.09
Pulmonary Obstructive Chronic	3.27
Gastroesophageal reflux disease (GERD)	1.63
Amount of Drug	
1-5 drug	6
6-10 drug	57
>10 drug	37

The number of type 2 DM patients shows that the number of women patients is greater than men. Other studies also showed that the number of women patients of type 2 diabetes DM (62%) more than men (38%). This is also in line with Khoirotun's research (2017) [5] where there are more women patients than men. There are more cases of type 2 diabetes in women due

to the role of hormonal factors experienced by women every month. In addition, obesity and pregnancy are also the risk factors. Hormonal changes play an important role in the lifestyle and physical activity of women. The prevalence of obese women is higher than men [7].

Apart from gender, age is also a risk factor for type 2 diabetes. The most age is at > 50 years. This study also showed that the majority of patients of type 2 DM were 60 years old [8]. Lira (2017) [9] also mentioned that from the research results the most age was > 50 years. Age is also a risk factor for DM. Someone with 45 years of age is even more at high risk of developing DM [2]. The prevalence of DM in developing countries is usually in the age range 45-64 years that fall into the productive age group. The function of pancreatic organs will also decrease with age. The effects of decreasing insulin secretion and decreasing insulin receptor sensitivity or insulin resistance have a major role in the development of old age. Age is related to interventions in the form of lifestyle changes in the management of DM in old age. Someone with old age is more difficult to change their lifestyle, especially the activities carried out become more limited [10]. Decreasing the function of pancreatic organs at an advanced age in the regulation of blood glucose causes the remaining pancreatic beta cells to remain active but the amount of insulin secretion decreases. Decreased muscle mass and vascular function are also associated with decreased sensitivity of peripheral cells to insulin resulting in an increase of blood sugar levels [11].

Most of the samples in this study had hypertension complications. Hypertension is a complication that often occurs in DM patients. The mechanism of type 2 DM is insulin resistance. This insulin resistance effects the pancreatic beta cells to continue producing insulin because the body signals that the amount of insulin is decreasing. This situation actually

illustrates that the initial damage to pancreatic beta cells is an early sign of DM. At the time of onset of DM, insulin secretion is no longer able to cover insulin resistance and cause significant damage to pancreatic beta cells. The period from the initial impairment of glucose tolerance to the onset of diabetes is marked by a state of hyperglycemia and hyperinsulinemia with insulin resistance. During this period, there is a risk of developing hypertension. In DM patients, the mechanism of vascular remodeling occurs. Vascular remodeling causes peripheral vascular resistance and causes an increase in blood pressure. In addition, the state of hyperglycemia causes impaired sodium and water reabsorption so that osmotic pressure increases causing blood pressure to increase [12].

Table 2. Profil of Drug Use of Antidiabetic in Type 2 Diabetes Mellitus With Complication

Antidiabetic	Frequency	Percentage
Single		
Metformin	13	24.52
Glimepiride	3	5.66
Gliquidone	5	9.43
Insulin glargine	5	9.43
Insulin lispro	1	1.88
Insulin aspart	16	30.18
Insulin gluisine	8	15.09
Insulin novomix	1	1.88
Pioglitazone	1	1.88
Combination		
Insulin (Long acting and Rapid acting)	33	54.11
Metformin and Gliquidone	4	6.55
Metformin and Insulin gluisine	1	1.63
Gliquidone and Acarbose	2	3.27
Metformin and Glimepiride	10	16.39
Metformin and Glibenclamide	4	6.55
Glimepiride and Acarbose	3	4.91
Acarbose and Insulin Gluisine	1	1.63
Gliquidon and Insulin glargine	1	1.63
Metformin and Pioglitazone	1	1.63
Acarbose and Metformin	1	1.63

The drug usage profile of 100 samples shows that the most used was combination drugs (56%) with the most types were the combination of insulin long acting insulin and rapid acting

insulin as much as 54.11%. While the use of a single drug is only 43% with the most single drug type is insulin aspart (30.18%). There is 1 patient who did not get antidiabetic.

The use of drugs also contributes to the increased risk of complications in people with DM. The use of drugs for a long time causes the risk of experiencing side effects to increase. One antidiabetic that is widely used because of its cost effectiveness is the sulfonylureas, especially glibenclamide. Sulfonylureas, especially glibenclamide, can increase the risk of cardiovascular disorders and hypoglycemia [13].

The most antidiabetic use in this study is a combination of long acting and rapid acting insulin and the use of insulin rapid single. Insulin is one type of antidiabetic with intravenous preparations. Some studies say that the use of insulin provides benefits for people with DM. The use of a combination of insulin seems to reduce the incidence of hypoglycemia even up to 80% after 1 month of use [14] and decrease the incidence of hypoglycemia by 24% and decrease the incidence of nocturnal hypoglycemia by 31% during 26 weeks of use [15].

The amount of drug use in this study was mostly from 6 to 10 types of drugs for 1 patient. DM sufferers with complications tend to use more drugs. Old age is also a risk factor for polypharmacy. Polypharmacy can cause decreased adherence [16], increase the risk of macrovascular complications, prolong hospitalization and increase mortality [17].

Analysis of the incident of DRPs was carried out using criteria from PCNE Vol 6.2 2010 and was analyzed by literature. The results of the analysis showed that the highest incidence of DRPs was drug interactions 94.62%. Drug interactions are also analyzed based on severity level. The highest severity level of interactions was moderate at 80.9%.

There was some drugs that interacted with antidiabetic such as increasing therapeutic effects and hyperglicemic risks.

Table 3. Distribution of Drug Related Problem in Type 2 Diabetes Mellitus With Complication

Drug Related Problems	Frequency of Case	Percentage
Sub-therapeutic dose	3	0.48
Overdose	18	2.93
Drug Interaction	581	94.62
Indication without drug	9	1.46
Drug without indication	3	0.48

From the results of the analysis of DRPs it appears that the most common occurrence is drug interactions with the most severity is moderate. Other studies on DRPs show that the most common category of DRPs in type 2 DM is drug interactions, which is 60% of 45 type 2 DM patients [9] and the results also show that DRPs are the most drug interactions, namely 45.6% of 81 type 2 DM patients [18]. Drug interactions are related to the amount of drug used. Many complications increase the number of drugs used. The more the number of drugs used, the higher the risk of drug interactions [19]. Some studies also mention that polypharmacy is associated with a high risk of drug interactions, decreased blood sugar control, and the lack of achievement of therapeutic effects [20],[21]. Statistical analysis was also carried out to determine the effect of the amount of drug use on the incidence of DRPs which showed there was an influence of the amount of drug use on the incidence of DRPs with $p = 0.002$. This shows that the increasing number of drug use, can increase the risk of DRPs.

One type of antidiabetic that causes drug interactions in this study is the combination of Furosemide and Insulin. The combination of the two drugs causes an interaction with moderate severity where Furosemide can cause disruption of blood glucose control and reduce the effectiveness of insulin. In addition, Furosemide also interacts with other antidiabetic drugs

such as Acarbose with moderate severity which can cause disruption of blood glucose control and reduce the effectiveness of Acarbose. Research suggests that the combination of furosemide with antidiabetic cytotoxic, insulin and sulfonylureas can cause interactions with moderate severity, pharmacodynamically and should be avoided. Furosemide can reduce the effects of oral antidiabetic and insulin so that it can increase the risk of hyperglycemia, glucose intolerance, and exacerbation of diabetes by increasing blood sugar levels [22].

Other interactions can be seen from the use of antidiabetics such as metformin with phenytoin. The use of these two drugs can interact with significant moderate severity. The mechanism that occurs is pharmacokinetic interaction where the use of both drugs can cause a decrease in antidiabetic effects. This can cause hyperglycemia, hypoinsulinemia and glucose intolerance. Some sulfonylureas used together with phenytoin can increase the concentration of phenytoin in the blood and reduce metabolism by competitive inhibition of cytochrome CYP 450 2C9 and 2C19 [23].

Antidiabetics are also seen to interact with steroidal analgesics such as methylprednisolone and metformin with moderate severity where methylprednisolone can interfere with blood glucose control and reduce the effectiveness of metformin [23]. Drugs that interact a lot with antidiabetic drugs such as insulin are angiotensin receptor blocker, aspirin, and angiotensin converting enzyme inhibitors and beta blockers [19].

Other studies also revealed that there were interactions of the use of Insulin and Furosemide in 10 cases and the use of insulin with methylprednisolone with as many as 1 case. Insulin also interacts with aspirin with moderate severity. A study states that the use of insulin and aspirin which is a group of salicylic acid causes pharmacodynamic interactions that are

additive. Thus, it can increase the effects of insulin thereby reducing the risk of hypoglycemia [24].

Based on the results of the study, examples of drug interactions with a major degree of significance were most common in the use of clopidogrel and omeprazole. The use of these two drugs together can cause interactions with pharmacokinetic mechanisms. This mechanism is mediated by cytochrome CYP 2C19 in which omeprazaloe inhibits this enzyme thereby reducing the steady state and clopidogrel concentration in the body thereby reducing the therapeutic effect of clopidogrel [25].

DRPs also occur in the drug dosage category given. There are cases where the dose of the drug is given below the usual dose range or the frequency of use is less so it does not produce an effect. An example of such a case is the use of a single Digoxin 0.25 mg every 24 hours. Whereas according to the Drug Information Handbook is 0.75-1.5 mg. Sub-therapeutic doses can result in low blood concentrations of the drug which results in the failure to achieve therapeutic effects. Conversely, there are cases of overdose such as Ceftriaxone 2 grams - every 12 hours, ciprofloxacin 500 mg, every 12 hours and simvastatin 20 mg, every 12 hours. The dosage that should be given is for Ceftriaxone 1-2 gr/day, Ciprofloxacin 250-500 mg/day, and Simvastatin 10-20 mg/day. Overdose can cause high concentrations of drugs in the blood, increased half-life, and can cause a risk of toxicity.

In addition, it can also lead to an increased risk of side effects. Other DRPs that also occurred in this study were indications without drugs. Other studies suggest that type 2 DM patients with hypertension need therapy to prevent mortality, morbidity and prevent hospitalization and disability. DM patients with hypertension are advised to use

drugs of choice such as the angiotensin converting enzyme inhibitor (ACEI) group or Angiotensin Receptor Blocker (ARB) [2].

Drugs without indications were also seen in this study. Some studies also mention that drugs without indications are commonly found as DRPs [26]. Some drugs are prescribed but there is no clear indication of the drug, such as complaints and symptoms are not appropriate, history of the disease is absent, and other supporting data also does not indicate the appropriate conditions. The results of the statistical analysis of the effect of the drug use amount on the incident of DRPs with Chi square showed that there was a significant effect (p = 0.002).

CONCLUSION

The DRPs that occur include dose inaccuracy which includes sub-therapeutic doses of 0.48% and doses above therapy of 2.93%. Indications without drugs 1.48% and drugs without indications 0.48%. The biggest DRPs occurred in the category of drug interactions that is 94.62%. There is an influence between the amount of drug use on the incident of DRPs (p = 0.002).

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