PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS AMONG PROLANIS TYPE 2 DIABETES PATIENT WITH HYPERTENTION IN PRIMARY HEALTH CARE: CROSS SECTIONAL STUDY

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ABSTRACT

Potential drug–drug interactions (pDDIs) are important factors resulting in adverse drug reactions or therapeutic failure. Therefore, pDDIs need to be identified to prevent the related risk and improve drug safety. The objective of this study was to assess the prevalence of pDDIs among Prolanis type 2 diabetes patients with hypertension. Additionally, this study aims to categorize and rate the identified pDDIs according to mechanism, severity and level of significance. This cross-sectional study was conducted at Kramat Jati District primary health care. Patient medical records from January to June 2018, were analysed using Drug Interaction Facts and Stockley's Drug Interaction for pDDIs with a total 138 patients identified. pDDIs were detected in 35 patients (25.4%), with a total 57 interactions. They were clinically relevant with major (42.1%) in severity and refer to level one of significance (42.1%). The interaction type was unknown (64.9%), pharmacodynamic (64.9%) and pharmacokinetic (12.2%) respectively. The most common interaction was amlodipine-simvastatin in 19 cases (33.3%). Prolanis type 2 diabetes patients with hypertension were at risk to pDDIs, particularly to major pDDIs. Screening of prescriptions and medical records for pDDIs also monitoring of pharmacotherapy in terms of response and associated adverse drug events will contribute to patient safety.

Keywords: potential drug-drug interactions; primary health care; Prolanis, type 2 diabetes; hypertension

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INTRODUCTION

Prolanis, which stands for Program Pengelolaan Penyakit Kronis, is a proactive health care service system which is design to fully ease communication and integrated between patients, health facilities, and Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan. Prolains aims to maintain health condition of BPJS Kesehatan participants who suffer from chronic diseases in order to achieve optimal quality of life with effective and efficient cost. Prolanis targeted to all BPJS Kesehatan participants with chronic diseases (including type 2 diabetes mellitus and hypertension) (BPJS, 2014).

Diabetes is a serious illness that become threat to global health, neither socioeconomic status nor national boundaries. The latest data published in the International Diabetes Federation (IDF) shows that 463 million adults currently live with diseases. Without sufficient action to address this serious condition, 578 million people predicted to suffer diabetes by 2030. Additionally, number of people suffer will jump to staggering 700 million by 2045 (IDF, 2022). The World Health Organization reported that about 1.5

million people died from diabetes in 2012 and additional 2.2 million deaths due to increased risk of cardiovascular diseases and other related condition to hyperglycaemia (Perkeni, 2019). Riset Kesehatan Dasar (Riskesdas) in 2018 explained that prevalence of national diabetes in Indonesia was 8.5%, which means around 20.4 million population were affected by diabetes (Balitbangkes, 2018).

Hypertension is a common comorbidity in type 2 diabetes patients, with a prevalence of up to two-thirds of the population, and it may be present by the time type 2 diabetes is diagnosed or even before the onset of hyperglycaemia. Hypertension enhances the risk of cardiovascular disease in type 2 diabetes patients (ADA, 2017).

Type 2 diabetes patients with hypertension often receive multiple medications and could lead to the occurrence of polypharmacy. Polypharmacy (≥5 concurrent drugs) is an important factor in drug interactions which is influencing drug-related problems (DRPs). A high prevalence of DRPs has been observed in type 2 diabetes patients (Mukete B. N & Ferdinand, K.C. 2016). DRPs may lead to suboptimal blood pressure which can contribute to significant morbidity or mortality, prolonged hospitalization, and increased health care expenditure if left unresolved (Enumula, et.al, 2021).

Drug interactions are major problem in pharmacotherapy, which can lead to unwanted therapy failure. Therefore, in clinical practice, patient safety is an important thing that must be improved by periodically identifying the drug interactions by pharmacists as efforts to remind members of other health care teams (Abu Bakar et al, 2015; Muti & Anindya, 2021). This study aimed to assess the prevalence of potential drug-drug interactions (pDDIs) among Prolanis type 2 diabetes patients with hypertension. Additionally, this study aims to categorize and rate the identified pDDIs according to mechanism, severity level and significance level.

MATERIALS AND METHODS

a. Materials

Administrative permission from Kramat Jati District primary health care was obtained in order to access patient's medical records. Data regarding patient's demographics, diagnoses, medication therapy, signs and symptoms and laboratory tests were collected.

b. Methods

This study was a retrospective cross-sectional study, conducted in the outpatient ward of Kramat Jati District primary health care in Jakarta, Indonesia. Ethical clearance and permission to collect data has been approved by administrative from Kramat Jati District Primary Health Care Jakarta. Total of 138 outpatients who were admitted to the hospital between January until June 2018 were included in the study. The inclusion criteria were 1) adult patients (≥26 years), 2) diagnosed with at least type 2 diabetes and hypertension, 3) Prolanis patients, 4) prescribed with at least one oral antidiabetic agent and antihypertensive. Profiles were excluded if they were incomplete with respect to relevant data required for this study.

All medications prescribed were evaluated for pDDIs using Drug Interaction Facts and Stockley's Drug Interaction. The overall prevalence of pDDIs and prevalence based on the mechanism, severity level and significance level have been reported and identified.

Descriptive statistics were used for presenting data in the form of frequencies and percentages.

RESULT

Most of the patients were female (103, 74.6%). The majority of the patients aged above 56 years of age (100, 72.5%) and patient's age mean was 61.3±8.4 years. It suggested that older patients with hypertensive diabetic admitted to the Prolanis outpatient ward compare to younger patients. Majority of hypertension cases found

classified as stage I hypertension. Patients have polypharmacy found that five medications were prescribed to majority patients (70, 50.7%). Patients experienced most pDDIs were taking a greater number of prescribed drugs. The patient's characteristics were summarized in **Table 1.**

Table 1. Patient's Characteristics

Characteristics	Patients: n (%)
Gender	
Male	35 (25.4)
Female	103 (74.6)
Age (years)	
36-45	1 (0.7)
46-55	37 (26.8)
56-65	55 (39.9)
>65	45 (32.6)
Prescribed medicines per patients	
2	15 (10.9)
3	40 (29.0)
4	13 (9.4)
≥5	70 (50.7)
Hypertension classification (mmHg)	
Stage II (BP ≥160/ >100)	20 (14.5)
Stage I (BP 140-159/ 90-99)	58 (42.0)
Prehypertension (BP 120-139/ 80-89)	47 (34.1)
Normal	13 (9.4)

Various oral antidiabetic agents were prescribed to the patients **(Table 2)**. About 81 patients (58.7%) received dual therapy, with the majority of patients receiving metformin and glimepiride combination (68, 49.3%). The rest, 57 patients (41.3%) received monotherapy.

Table 2. Medication used in Prolanis type 2 diabetes patients with hypertension (n=138)

Characteristics	Patients: n (%)
Oral antidiabetic agent	
Metformin	57 (41.3)
Metformin + glimepiride	68 (49.3)
Metformin + glyburide	10 (7.2)
Metformin + gliclazide	2 (1.5)
Gliquidone + acarbose	1 (0.7)
Antihypertensive agent	
Amlodipine	114 (82.6)
Valsartan	4 (2.9)
Telmisartan	2 (1.5)
Candesartan	1 (0.7)
Amlodipine + telmisartan	8 (5.8)
Amlodipine + captopril	3 (2.2)
Amlodipine + valsartan	2 (1.5)
Amlodipine + candesartan	1 (0.7)
Valsartan + bisoprolol	1 (0.7)
Bisoprolol + nifedipine + telmisartan	1 (0.7)
Bisoprolol + amlodipine + valsartan	1 (0.7)

In the management of hypertension, clinicians preferred to use monotherapy (121, 87.7%) with the use of amlodipine, which become most frequent used antihypertensive drug (114, 82.6%). The choice of antihypertensive agent was inconsistent with the evidence-based guideline (ADA, 2017; James et al., 2014; Mancia et al., 2013). Instead of prescribing angiotensin converting enzyme or angiotensin receptor blocker, clinicians preferred to prescribe calcium channel blocker. Fifteen patients (10.9%) received dual therapy and two patients (1.4%) received triple therapy.

Table 3. Most frequently identified interactions, their levels and mechanisms

First drug	Second drug	n (%)	Severity level	Significance level	Mechanism
Amlodipine	Simvastatin	19 (33.3)	Major	1	Increased simvastatin plasma concentrations
Simvastatin	Glimepiride	10 (17.5)	Minor	5	Increased glimepiride plasma concentrations
Aspirin	Glimepiride	6 (10.5)	Moderate	2	Aspirin reduces basal plasma glucose levels and enhances insulin secretion. Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose
Na diclofenac	Aspirin	3 (5.3)	Major	1	Competitive inhibition of the acetylation site of cyclooxygenase in the platelet is suspected

DISCUSSION

Drug-drug interaction can be defined as the phenomenon that occurs when the effects or pharmacokinetics of a drug are altered by prior administration or coadministration of a second drug (Thürmann, & Petra A, 2020; Anker et., al, 2018; Hartshorn & Tatro, 2012). The pDDIs concept refers to the possibility a drug has to alter the effects of another when both are simultaneously administered (Alvim et al., 2015). In this study, total of 138 patients were analysed during the study period, of which 35 (25.4%) patients showed 57 pDDIs. Prevalence of pDDIs in this study is higher compared with that reported by similar studies in Malaysia and Bandung (16.3-17.2%) (Huri & Wee, 2013; Zazuli et al., 2017), but lower compared to studies conducted in Solo, South Tangerang and Palu (31%-85.2%) (Hidayah et al., 2018; Saibi et al., 2018; Nurlaelah et al., 2015). This inconsistency might be caused by varied study population, study design, pattern of drug prescribing/ utilization, disease trends and type of DDIs screening tools.

Out of the total pDDI identified, (7, 12.3%) were pharmacokinetic interactions, (13, 22.8%) were pharmacodynamic interactions and (37, 64.9%) interaction having unknown mechanism of drug interaction (**Figure 1**). The most frequent pharmacokinetic interaction occurred is the metabolism level including prednisone and aspirin (2, 3.52%), ranitidine and glyburide (1, 1.75%) also dexamethasone and aspirin (1, 1.75%). The most frequent pharmacodynamic interaction occurred was between aspirin and glimepiride (6, 10.5%) cases; and unknown interaction which included amlodipine and simvastatin (19, 33.3%) cases.

Severity of pDDIs and their corresponding scientific evidence have a decisive role in the monitoring and management for adverse events related to its interactions (Ismail et al., 2018). The potential severity of the interaction is particularly important in assessing the risk versus benefit of therapeutic alternatives. With appropriate dosage adjustments or modification of the administration schedule, the negative effects of most interactions can be avoided (Thürmann, & Petra A, 2020; Anker et., al, 2018; Hartshorn & Tatro, 2012). In our study, the most common severity pDDIs is major (24, 42.1%) (**Figure 1**). In major severity, the effects are potentially life-threatening or inducing permanent damage; addition of treatment, hospitalization, or an extended hospitalization might be necessary.

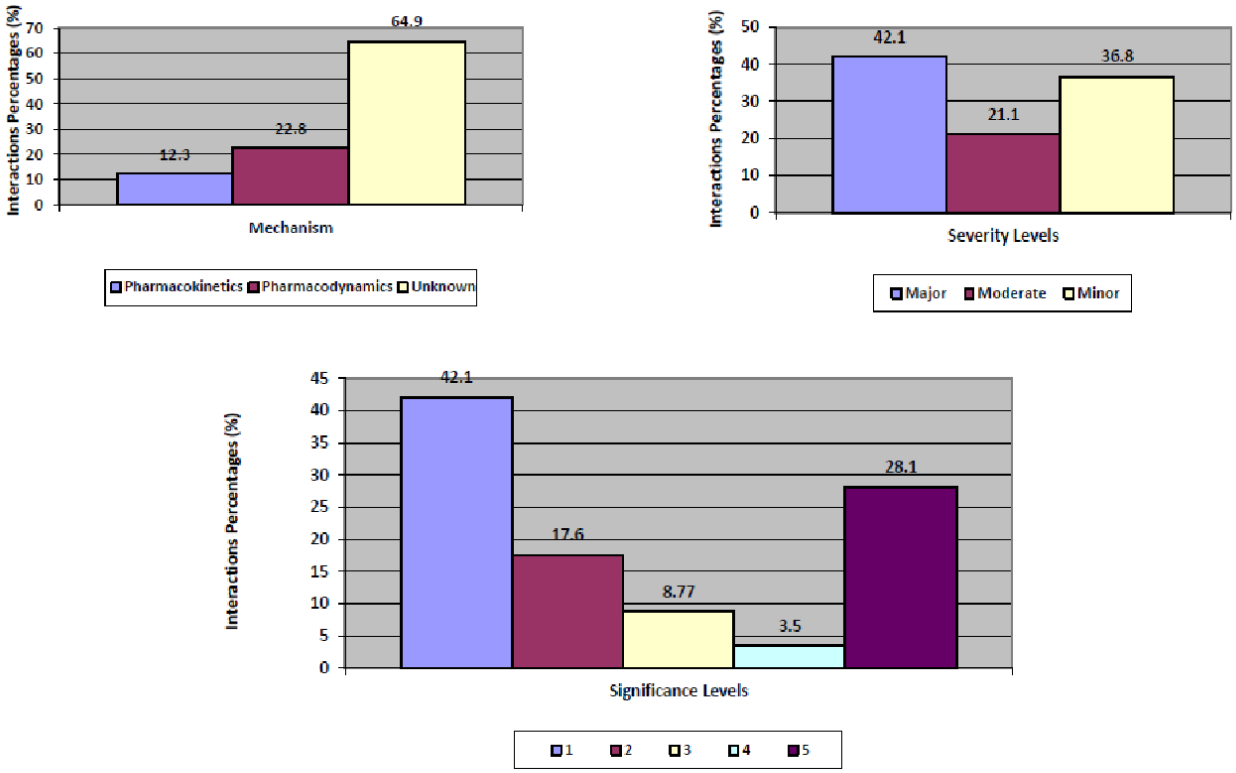

Figure 1. Prevalence of Mechanism, Severity levels and significance levels of pDDIs

During evaluation of any potential drug interaction, the primary concern is the clinical relevance or significance of the interaction. Significance relates to the type and magnitude of the effect and, subsequently, to the necessity of monitoring the patient or altering therapy to avoid potentially adverse consequences. The primary factors that define clinical significance include significance rating; the time of onset of the effects of the interaction; the potential severity of the interaction; and the documentation that an interaction occurs clinically (Thürmann, & Petra A, 2020; Anker et., al, 2018; Hartshorn & Tatro, 2012). In our study, the most significant pDDIs belong to level one (24, 42.1%) (**Figure 1**). Level one means a severe and well-documented interaction.

In our study, most common pDDIs happen between amlodipine and simvastatin (19, 33.3%). This interaction is categorized as major severity with level one significance. The mechanism of the interaction is unknown, but the effect of this interaction causes an increase in the plasma concentration of simvastatin.

Calcium channel blockers (CCBs) selectively inhibit voltage-gated L-type channels on cardiac myocytes, cardiac cells in the sinoatrial and atrioventricular nodes, and vascular smooth muscle cells peripherally. CCBs have a significant role in the treatment of several cardiovascular conditions such as hypertension, chronic stable angina, and supraventricular arrhythmias (Khodenva, et al., 2016; Fahed et al., 2021; Crea, Luizzo, et al., 2013). Because of clearly defined cardiovascular benefits, CCBs are often co-prescribed in patients treated with statin therapy (ADA, 2017).

According to American Heart Association (AHA) (2016) scientific statement, amlodipine is a substrate of CYP3A4 and its plasma concentrations may be affected by inhibitors or inducers of this enzyme. Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared with simvastatin alone.

However, co-administration of amlodipine with 80 mg atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin. In the ALLHAT-LLT trial (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Treatment), 1122 patients (21.7%) took amlodipine in combination with pravastatin, and no incidence of muscle-related toxicity was reported. Pharmacokinetic data suggest a minor increase in statin exposure with co-administration of either lovastatin or simvastatin with amlodipine, and these combination therapies may be considered. For adult patients on stable therapy with simvastatin 80 mg daily (a dose that is no longer recommended for general use), clinicians should change to a non-CYP3A4 statin such as pravastatin, rosuvastatin, or pitavastatin if therapy with diltiazem or verapamil is initiated (AHA, 2016)..

Our study has some limitations because of the small number of sample sizes and short period of study. We also did not measure the outcome of the pharmacist intervention. The small number of patients calls for a larger and longer period of confirmatory study.

CONCLUSION

Substantial prevalence of pDDIs has been observed in Prolanis type 2 diabetes with hypertension at Kramat Jati District primary health care setting (25.4%). Interactions of major-pDDIs found to be more common, however, moderate and minor-pDDIs also observed in considerable numbers. List of most frequent identified interactions will efficiently support the selective screening and monitor patients for pDDIs, moreover association with negative consequences. To improve patient's safety and outcome of therapy, specific strategies are essential to be implemented, these includes software-based screening of pDDIs, patient education and counselling, and regular follow-up.

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