Drug-Related Problems in Type 2 Diabetic Patients with Hypertension: A Prospective Study

Zulfan Zazuli, Azmi Rohaya, I Ketut Adnyana

Pharmacology and Clinical Pharmacy Research Group, School of Pharmacy Institut Teknologi Bandung, Indonesia

ABSTRACT

Introduction: Type 2 diabetic patients whom also diagnosed with hypertension often received a complex medication regimen. The situation may lead to the increased risk of drug-related problems (DRPs). The aim of the study was to identify the DRPs in type 2 diabetic patients whom also diagnosed with hypertension in the following domains: problems, causes, and interventions. **Methods:** The prospective study was conducted from October to December 2015 at a secondary-care hospital in Indonesia involving 90 inpatients who meet the predetermined inclusion criteria. Identification and classification of DRPs were based on the Pharmaceutical Care Network Europe (PCNE) version 5.01. Correlation among subject's independent factors and the number of DRPs was also analysed. **Results:** As many as 261 DRPs were identified, averaging 2.88 (SD=0.23) problems per patient. Drug choice problem was the most frequent problems (n=144, 55.17%) while drug/dose selection was the main causes (n=184, 62.16%). From a total 155 interventions, the majority was conducted at patient /carer level (n=94, 60.65%). The bivariate analysis showed that the number of medications (r=0.49, p<0.01) and the length of stay (r=0.25, p<0.05) significantly correlated with the number of DRPs. Based on linear regression analysis, the number of medications significantly predicted the number of DRPs (β=0.50, p<0.001). **Conclusion:** Since the risk of DRPs in type 2 diabetic and hypertension patients relatively high, early detection by the pharmacist is needed to ensure the safety and effectiveness of drug therapy.

Key words: Type 2 diabetes mellitus, hypertension, drug-related problems, clinical pharmacy services, medication error

Correspondence:
Zazuli Zulfan,
Pharmacology and Clinical Pharmacy Research Group, School of Pharmacy Institut Teknologi Bandung, Indonesia.
E-mail: zulfan@fa.itb.ac.id

Access this article online
Website: www.jbclinpharm.org
Quick Response Code:

INTRODUCTION

Diabetes has become a global health problem and economic burden worldwide. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades. World Health Organization (WHO) estimate that adults who were living with diabetes increase from 108 million in 1980 to 422 million in 2014.[1] A study reported that global age-standardised diabetes prevalence increased from 4.3% in 1980 to 9.0 in 2014 in men, and from 5.0% to 7.9% in women.[1,2] Diabetes responsible for causing 1.5 million deaths in 2012.[1] A reviewed studies addressed a large economic burden caused by diabetes, most directly affecting patients in low-middle income countries.[3] Diabetic patients often accompanied by hypertension. This comorbid may lead to serious cardiovascular complications e.g., heart attack, stroke, and kidney failure.

The diabetic patients are vulnerable in experiencing drug-related problems. Moreover, diabetes mellitus type often accompanied by various comorbidities. The situation results in increasing the risk of drug-related problems (DRPs). Pharmaceutical Care Network Europe described a drug-related problem as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.[4] Previous study in Malaysia showed that each diabetic patient experienced at least one DRP[5,6] while a study in Denmark showed at least four DRPs per patient.[7] However, Indonesia has a lack of studies on DRPs in such patients, particularly on secondary health care facility setting.

The study aims to identify the DRPs in type 2 diabetic patients whom also diagnosed with hypertension in the following domains: problems, causes, and interventions. The study also determines the factors that were significantly associated with DRPs in type 2 diabetic patients with hypertension. The result of the study will provide pharmacist a clear description concerning the pattern of DRPs in such patients and would be helpful for pharmacists to create the strategy to prevent such DRPs happened.

SUBJECTS AND METHODS
Study design and setting

The prospective study was conducted in the inpatient ward of a secondary care hospital in Cimahi, West Java, Indonesia following research approval by the hospital education and ethics committee No. 070/2162/RSUD-CBBT.

Subjects

A total 90 inpatients whom admitted to the hospital between October 1st until December 31st, 2015 and fulfilled the inclusion criteria were included in the study. The inclusion criteria were 1) adult patients (>18 years old), 2) diagnosed with at least type 2 diabetes mellitus and hypertension, 3) prescribed with at least one antidiabetic agent and antihypertension while the exclusion criteria were 1) diagnosed with type 2 diabetes mellitus and hypertension but not prescribed any antidiabetic agent and antihypertension agent, 2) pregnant during the hospitalization period.

DRPs identification and classification

The hospital pharmacists assessed the DRPs based on clinical judgment supported by updated evidence-based disease management guideline and literature. The identified DRPs was classified based on the Pharmaceutical Care Network Europe (PCNE) Classification for Drug-related problems V 5.01[4] The causes of DRPs and type of intervention by pharmacists were also recorded.

STATISTICAL ANALYSIS

Categorical variables were shown as frequencies and percentages; while numerical variables were described using means and standard deviation. Bivariate analysis was conducted to determine factors that were significantly associated with DRPs in type 2 diabetic patients with hypertension. Statistical analyses were performed using a data analysis freeware.

RESULTS

Demographic characteristics

As many as 90 patients meet the inclusion criteria of the study. Most of the patients were female (n=74, 82.8%) and the rest were male. The majority of the patients were under 56 years of age (n=52, 57.8%) confirming that the onset of type 2 diabetic patients with hypertension was shifting to the younger age population. The mean of patients' age was 57.73 years (SD=10.14).

Clinical characteristics

Majority of hypertension cases found of the patients (48; 53.3%) was classified as stage II hypertension. Most of the type 2 diabetic subjects had one comorbidity (32; 35.6%) beside hypertension. As many as 6 to 10 medications were prescribed to majority subjects (56; 62.2%). In addition, as many as 58 subjects (64.4%) admitted to hospital for ≤ 7 days. Most of the patients were shown improvement (84; 93.3%) when they were discharged from the hospital. The patients' clinical characteristics were summarized in Table 1.

Kidney disease was the most common comorbidities found in the type 2 diabetic with hypertension patients (47; 52.2%) followed by heart disease (25, 27.8%) and stroke (24; 26.7%).

Medication used in type 2 diabetic with hypertension patients

Various antidiabetic agents prescribed to the subjects. As many as 38 subjects (74.5%) received dual antidiabetes therapy, with majority subjects prescribed with insulin glargine and insulin aspart

combination (15; 29.4%). Nine patients (17.6%) received monotherapy while only four patients (7.8%) received triple therapy.

Clinicians preferred dual therapy in the management of hypertension (26; 43.3%) with amlodipine-valsartan combination become the most frequent antihypertensive prescribed (17; 28.3%). The choice of antihypertensive agent was inconsistent with the evidence-based guideline.[8-10] Instead of prescribing angiotensin converting enzyme or angiotensin receptor blocker, clinicians preferred to prescribed calcium channel blocker. 23 subjects (38.3%) received monotherapy, while amlodipine became the most preferred antihypertensive agent (15; 25%).

Drug-related problems

Problems concerning drug choice were the most common (55.2%) DRPs encountered with "no drug prescribed but clear indication" being the most frequent problem (25.3%). Overall, as many as 261 DRPs were identified, averaging 2.88 (SD=0.23) problems per patient. The details of the type of DRPs found in patients can be seen in Table 2.

Most of the DRPs were caused by drug/dose selection (62.2%) with "inappropriate drug selection" being the most common cause (25.3%) followed by "synergistic/preventive drug required and not given" (22.3%) (Table 3). "Drug use process" was the second most frequent cause (26%).

Table 4 shows that most of the pharmacist's intervention to resolve DRPs

Table 1: Patient's clinical characteristics

Parameters	n (%)
Hypertension classification	
Stage II (TD=>160/>100 mmHg)	48 (53.3)
Stage I (TD=140-159/90-99 mmHg)	29 (32.2)
Pre-hypertension (TD=120-139/80-89 mmHg)	13 (14.0)
Number of comorbidities	
1	32 (35.6)
2	30 (33.3)
3	16 (17.8)
Without comorbid	8 (8.9)
4	3 (3.3)
5	1 (1.1)
Number of medications received	
6-10	56 (62.2)
11-15	20 (22.2)
>15	8 (8.9)
1-5	6 (6.7)
Length of stay	
≤ 7 days	58 (64.4)
8-14 days	27 (30.0)
≥ 15 days	5 (5.6)
Discharge outcome	
Improvement	84 (93.3)
Death	6 (6.7)

Table 2: Type of DRPs found on patients

Code	Detailed classification	Frequency (%)
P1	**Adverse reactions**	**30 (11.4)**
P1.1	Side effect suffered (non-allergic)	23 (8.8)
P1.2	Side effect suffered (allergic)	4 (1.5)
P1.3	Toxic effects suffered	4 (0.8)
P2	**Drug choice problem**	**144 (55.2)**
P2.1	Inappropriate drug (not most appropriate for indication)	30 (11.5)
P2.2	Inappropriate drug form (not most appropriate for indication)	0 (0)
P2.3	Inappropriate duplication of therapeutic group or active ingredient	20 (7.7)
P2.4	Contra-indication for drug (incl. Pregnancy/breast feeding)	4 (1.5)
P2.5	No clear indication for drug use	24 (9.2)
P2.6	No drug prescribed but clear indication	66 (25.3)
P3	**Dosing problem**	**28 (10.7)**
P3.1	Drug dose too low or dosage regime not frequent enough	19 (7.3)
P3.2	Drug dose too high or dosage regime too frequent	7 (2.7)
P3.3	Duration of treatment too short	1 (0.4)
P3.4	Duration of treatment too long	1 (0.4)
P4	**Drug use problem**	**11 (4.2)**
P4.1	Drug not taken/administered at all	9 (3.5)
P4.2	Wrong drug taken/administered	2 (0.8)
P5	**Interactions**	**47 (18.0)**
P5.1	Potential interaction	45 (17.2)
P5.2	Manifest interaction	2 (0.8)
P6	**Others**	**1 (0.4)**
P6.1	Patient dissatisfied with therapy despite taking drug(s) correctly	0 (0)
P6.2	Insufficient awareness of health and diseases (possibly leading to future problems)	0 (0)
P6.3	Unclear complaints. Further clarification necessary	0 (0)
P6.4	Therapy failure (reason unknown)	1 (0.4)
	Sum Total	**261 (100)**

Table 3: Classification of DRPs causes found on patients

Code	Detailed classification	Frequency (%)
C1	**Drug/Dose selection**	**184 (62.2)**
C1.1	Inappropriate drug selection	75 (25.3)
C1.2	Inappropriate dosage selection	13 (4.4)
C1.3	More cost-effective drug available	0 (0)
C1.4	Pharmacokinetic problems, incl. ageing/ deterioration in organ function and interactions	0 (0)
C1.5	Synergistic/preventive drug required and not given	66 (22.3)
C1.6	Deterioration/improvement of disease state	0 (0)
C1.7	New symptom or indication revealed/presented	0 (0)
C1.8	Manifest side effect, no other cause	30 (10.1)
C2	**Drug use process**	**77 (26.0)**
C2.1	Inappropriate timing of administration and/or dosing intervals	17 (5.7)
C2.2	Drug underused/under-administered	19 (6.4)
C2.3	Drug overused/over-administered	8 (2.7)
C2.4	Therapeutic drug level not monitored	22 (7.4)
C2.5	Drug abused (unregulated overuse)	1 (0.3)
C2.6	Patient unable to use drug/form as directed	10 (3.4)
C3	**Information**	**16 (5.4)**
C3.1	Instructions for use/taking not known	13 (4.1)
C3.2	Patient unaware of reason for drug treatment	3 (1.0)
C3.3	Patient has difficulties reading/understanding Patient Information Form/Leaflet	0 (0)
C3.4	Patient unable to understand local language	0 (0)
C3.5	Lack of communication between healthcare professionals	0 (0)
C4	**Patient/Psychological**	**17 (5.7)**
C4.1	Patient forgets to use/take drug	13 (4.1)
C4.2	Patient has concerns with drugs	0 (0)
C4.3	Patent suspects side-effect	3 (1.0)
C4.4	Patient unwilling to carry financial costs	0 (0)
C4.5	Patient unwilling to bother physician	0 (0)
C4.6	Patient unwilling to change drugs	0 (0)
C4.7	Patient unwilling to adapt life-style	1 (0.3)
C4.8	Burden of therapy	0 (0)
C4.9	Treatment not in line with health beliefs	0 (0)
C4.10	Patient takes food that interacts with drugs	0 (0)
C5	**Logistics**	**2 (0.7)**
C5.1	Prescribed drug not available (anymore)	2 (0.7)
C5.2	Prescribing error (only in case of slip of the pen)	0 (0)
C5.3	Dispensing error (wrong drug or dose dispensed)	0 (0)
C6	**Others**	**0 (0)**
C6.1	Other cause	0 (0)
C6.2	No obvious cause	0 (0)
	Sum Total	**296 (100)**

Table 4: Classification of interventions on DRPs found on patients

Code	Detailed classification	Frequency (%)
	No intervention	0 (0)
I1	**At prescriber level**	**43 (27.7)**
I1.1	Prescriber informed only	29 (18.7)
I1.2	Prescriber asked for information	0 (0)
I1.3	Intervention proposed, approved by Prescriber	9 (5.8)
I1.4	Intervention proposed, not approved by Prescriber	5 (3.2)
I1.5	Intervention proposed, outcome unknown	0 (0)
I2	**At patient/carer level**	**94 (60.7)**
I2.1	Patient (medication) counselling	60 (38.7)
I2.2	Written information provided only	0 (0)
I2.3	Patient referred to prescriber	0 (0)
I2.4	Spoken to family member/caregiver	34 (21.9)
I3	**At drug level**	**18 (11.6)**
I3.1	Drug changed	2 (1.3)
I3.2	Dosage changed	11 (7.1)
I3.3	Formulation changed	0 (0)
I3.4	Instructions for use changed	0 (0)
I3.5	Drug stopped	5 (3.2)
I3.6	New drug started	0 (0)
I.4	**Other intervention or activity**	**22 (14.2)**
I4.1	Other intervention	22 (14.2)
I4.2	Side effect reported to authorities	0 (0)
	Sum Total	**155 (100)**

DISCUSSION

Diabetes mellitus has become an emerging threat to Indonesia. In 2015, the International Diabetic Federation (IDF) stated that Indonesia was ranked 7th in countries with the largest numbers of people with diabetes. The IDF estimated that 10 million of Indonesian adults live with diabetes with national prevalence 6.2% [5.4-6.7].[11] In addition, the IDF also predicted that people with diabetes in Indonesia will rapidly increase to 16.2 million in 2040.[11] The risk of financial burden to the country newly established health system Jaminan Kesehatan Nasional (JKN) or National Health Insurance in the future should be considered. As a consequence, the country must work hard to prevent and combat the disease.

On the other hand, type 2 diabetic patients may encounter some problems to the patients related to their disease and medications. The majority of type 2 diabetic patients was accompanied with at least one comorbidities. One of the most common comorbidities was hypertension that may lead to other cardiovascular and cerebrovascular disease in the future. The situation may lead to higher risk of DRPs. This study showed that an average 2.88 DRPs (SD=0.23) problems per type 2 diabetic with hypertension patients while a Malaysian and Danish study showed an average 1.9 and 4.1 DRPs per patient respectively.[7] An Australian study showed that medication-related problems on diabetic patients were associated with 7.2% hospital admissions.[12] Not remembering to refill medications was the most commonly reported medication adherence problem in type 2 diabetic patients.[13]

We found that drug choice problem was the most frequent problems while a Malaysian study showed that the most common DRPs encountered were insufficient awareness of health and diseases.[5] For example, pharmacists found that no antihypertensive prescribed but clear indication of hypertension. Both our study and the previous study found that most of the DRPs were caused by drug/dose selection.

were conducted at patient / carer level (60.7%) by providing medication counseling and spoke to the family member/caregiver (38.7 and 21.9% respectively). Intervention at the prescriber level came in second with 27.7% with the majority on informing the prescriber (18.7%).

Factors that associated with DRPs in type 2 diabetic patients with hypertension

We try to determine the factors that were significantly associated with DRPs in type 2 diabetic patients with hypertension using bivariate analysis. Based on the analysis, we found that the number of medications (r=0.49, p<0.01) and the length of stay (r=0.25, p<0.05) significantly correlated with the number of DRPs. Based on linear regression analysis, the number of medications significantly predicted the number of DRPs (b=0.50, p<0.001).

We also determined that the number of medications and the length of stay significantly correlated with the number of DRPs. This finding was consistent with the previous study.[5] However, the previous study also found significant associations with renal impairment, cardiovascular disease, and elderly status. Our findings were similar to a study by Koth, *et al.* which is shown that among patients with polypharmacy, age and gender may not be as important as the number of drugs prescribed as predictors of experiencing a DRPs.[14] A study by Viktil *et al.* also stated that the number of DRPs per patient was linearly related to the number of drugs used on admission.[15]

The majority of the pharmacist intervention for DRPs resolutions were conducted at patient/carer level, such as providing counselling and education to the family. Pharmacists direct involvement on type 2 diabetic with hypertension patient therapy may provide a solution in early detection of DRPs. Previous research stated that the involvement of the clinical pharmacist in diabetic patients helps in identification and prevention of DRPs.[16] A comprehensive and a brief individually targeted intervention for patients with type 2 diabetes by pharmacist could improve implementation of drug therapy.[17] Moreover, pharmacist involvement in multidisciplinary healthcare team may promote quality improvement in safe medication management[18] and reduce medical cost.[19] The pharmacist may also use a checklist tool to assist them identify issues in therapy and management of their type 2 diabetes patients systematically and enable earlier intervention to improve metabolic control.[20] The intervention may lead to better therapeutic outcomes by rationalizing drug therapy. However, this study did not measure the outcome of the pharmacist intervention.

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

Key messages

The study successfully determines the pattern of drug-related problems in type 2 diabetic patients with hypertension. Moreover, it shows that the number of medications and the length of stay significantly correlated with the number of DRPs while the number of medications significantly predicted the number of DRPs.

REFERENCES

1. World Health Organization Global Report on Diabetes. 2016.

2. Collaboration NRF. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513-30.

3. Seuring T, Archangelidi O, Suhrcke M. The Economic Costs of Type 2 Diabetes: A Global Systematic Review. Pharmacoeconomics 2015;33:811-31.

4. Foundation PCNE. PCNE Classification for Drug related problems V 5.01.2006.

5. Zaman Huri H, Fun Wee H. Drug related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocr Disord 2013;13:1-12.

6. Zaman HH, Chai LL. Drug-related problems in type 2 diabetes mellitus patients with dyslipidemia. BMC Public Health 2013;13:1192.

7. Haugbølle LS, Sørensen EW. Drug-related problems in patients with angina pectoris, type 2 diabetes and asthma-interviewing patients at home. Pharmacy World and Science 2006;28:239-47.

8. Standards of medical care in diabetes: summary of revisions. Diabetes Care 2015;38 Suppl:S4.

9. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, *et al.* Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.

10. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, *et al.* 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159-219.

11. International Diabetes Federation Diabetes. Atlas, 7th edition. 2015.

12. Claydon-Platt K, Manias E, Dunning T. Medication-related problems occurring in people with diabetes during an admission to an adult teaching hospital: a retrospective cohort study. Diabetes Res Clin Pract 2012;97:223-30.

13. Odegard PS, Carpinito G, Christensen DB. Medication adherence program: adherence challenges and interventions in type 2 diabetes. J Am Pharm Assoc 2013;53:267-72.

14. Koh Y, Kutty FBM, Li SC. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. Ther Clin Risk Manag 2005;1:39-48.

15. Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol 2007;63:187-95.

16. Shareef J, Fernandes J, Samaga L. Assessment of clinical pharmacist interventions in drug therapy in patients with diabetes mellitus in a tertiary care teaching hospital. Diabetes Metab Syndr 2016;10:82-7.

17. Kjeldsen LJ, Bjerrum L, Dam P, Larsen BO, Rossing C, Søndergaard B, *et al.* Safe and effective use of medicines for patients with type 2 diabetes-A randomized controlled trial of two interventions delivered by local pharmacies. Res Social Adm Pharm 2015;11:47-62.

18. Zhao RY, He XW, Shan YM, Zhu LL, Zhou Q. A stewardship intervention program for safe medication management and use of antidiabetic drugs. Clin Interv Aging 2015;10:1201-12.

19. Chen JH, Ou HT, Lin TC, Lai ECC, Kao YHY. Pharmaceutical care of elderly patients with poorly controlled type 2 diabetes mellitus: a randomized controlled trial. Int J Clin Pharm 2016;38:88-95.

20. Van Roozendaal BW, Krass I. Development of an evidence-based checklist for the detection of drug related problems in type 2 diabetes. Pharm World Sci 2009;31:580-95.