International Journal of Public Health Science (IJPHS)
Vol.7, No.1, March 2018, pp. 59~64
ISSN: 2252-8806, DOI: 10.11591/ijphs.v7i1.11438

Identification of Potential Drug Interaction with Complementary and Alternative Medicines among Chronic Disease Outpatients

Nurul Maziyyah[1], Apri Nurdianto[2], Arsitania Nur Kun Fajria[3]
Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Yogyakarta, Indonesia

Article Info

Article history:

Received Jan 12, 2018
Revised Mar 8, 2018
Accepted Mar 25, 2018

Keyword:

Alternative
Chronic disease
Complementary
Drug interaction

ABSTRACT

Chronic diseases such as congestive heart failure (CHF) and chronic kidney disease (CKD) are related with multiple drug prescription which can lead to drug interaction. The high usage of complementary and alternative medicines (CAM) in Indonesians can also increase the risk for drug interaction. The objective of this study is to describe CAMs use and identify potential drug interaction with CAMs in CHF and CKD outpatients. The study is a cross sectional study. Data of prescribed drugs and CAMs consumed by the patients was collected by using medication reconciliation process. Data of routine CAMs and prescribed medicines were compared to identify potential drug interactions which were then classified based on their mechanism and significance. The result showed that 6,90 % of CHF patients and 25 % of CKD patients consumed CAMs. Potential drug interaction between the CAMs and the prescribed drugs was identified in 2.74% of patients consuming CAMs. Based on the mechanism, interaction was dominated by pharmacodynamics interaction (69.2%) while interaction significancy was various. It can be concluded that CAMs usage was more familiar in CKD patients compared to CHF patients. Potential drug interaction with CAMs was able to be identified through medication reconciliation process and should be taken into awareness by the healthcare team.

Corresponding Author:

Nurul Maziyyah,
Faculty of Medicine and Health Sciences,
Universitas Muhammadiyah Yogyakarta,
Lingkar Selatan Road, Tamantirto, Kasihan, Bantul, Special District of Yogyakarta, Indonesia.
Email: maziyyahnurul@yahoo.com; maziyyahnurul@umy.ac.id

1. INTRODUCTION

Drug Interaction is included in one of the Drug Related Problems (DRPs) which is still often seen nowadays in the clinical and community settings. One of the causes for the high incidence of drug interaction is patients receiving multiple drug prescription such as geriatric patients or patients with chronic diseases namely Diabetes Mellitus, hypertension, kidney failure, and heart failure. A study in a Central Public Hospital in Yogyakarta, Indonesia revealed a 59% of drug interaction occurence among inpatients and 69% in outpatients [1]. High percentage of drug interaction should lead to awareness to avoid significantly hazardous interactions.

The use of complementary and alternative medicines (CAMs) such as herbs and supplements has been familiar among Indonesian people. Result from a national survey noticed an increase in traditional medicine usage for self-medication from 15.6% in 2000 to 31.7% in 2001 [2]. A following survey in 2007 also revealed an increase of 23.1% in CAMs usage since 2000 [3]. The relationship between CAMs usage and drug interaction was studied by Tsai et al. which described 882 drug interaction with herbs and supplements, of which 240 were classified as major interaction [4].

High incidence of drug interaction among chronic disease patients and high CAMs usage among Indonesians should lead to a prevention strategy from healthcare providers. Pharmacist as one of the healthcare providers concerning in rational drug therapy must take the first step for this prevention strategy. Gathering important information of drug and CAMs usage through medication reconciliation process can be conducted in order to identify and prevent drug interaction in these patients which eventually could prevent medication errors caused by drug interaction [5]. This could be a beneficial support to physicians who usually meet difficulty in screening and detection process of drug interactions in patients' drug list [6].

This study is aimed to describe CAMs use and identify potential drug interaction between prescribed drugs and between CAMs with the prescribed drugs in congestive heart failure (CHF) and chronic kidney disease (CKD) outpatients through medication reconciliation process as the first step in preventing drug interaction.

2. RESEARCH METHOD

This study was conducted through a cross sectional design and has pass ethical clearance. Subjects recruited were outpatients visiting one of a private hospital in Special District of Yogyakarta, Indonesia from August to October 2014. Patients were enrolled into the study if they were diagnosed with either congestive heart failure or chronic renal disease and were willing to participate, verified by signing the inform consent provided by the researcher.

Medication reconciliation process was then conducted to the selected patients. Patients that met the inclusion criteria were interviewed to collect and gather up data of medication and CAMs usage (defined as herbs and dietary supplements) wether prescribed or non-prescribed by their doctor. Patients were requested to explain the name, dose, frequency, how, and when they consume the medication or CAMs.

Identification of potential drug interaction was done by comparing medication and CAMs used by the patients routinely before their visit to the hospital with medication obtained from the doctor. Literature study was held to verify the potential interactions, using mainly Drug Interaction Facts by Tatro (2010) and Stockley's Drug Interaction.

3. RESULTS AND ANALYSIS

3.1. Distribution of Patients

Patients selected for the study was divided into two subjects based on their main diagnosis which are Chronic Kidney Disease (CKD) patients or Congestive Heart Failure (CHF) patients. Seventy three patients met the inclusion criteria from both subjects. Distribution of patients' diagnosis can be seen in Figure 1.

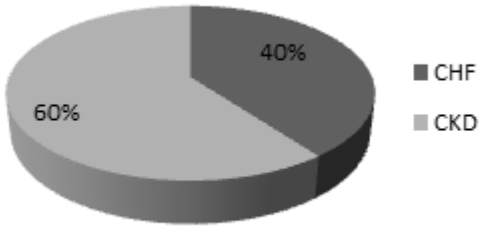

Figure 1. Distribution of Patients

From 73 patients, 29 patients (40%) were diagnosed with CHF while the rest of 44 patients (60%) were diagnosed with CKD. CHF and CKD patients are examples of chronic disease patients with a relatively high prevalence in Indonesia, especially in The Special District of Yogyakarta. Based on the National Primary Health Research (*Riset Kesehatan Dasar*) published in 2013 by The Indonesian Ministry of Health, Yogyakarta had the highest prevalence of diagnosed CHF patients with a percentage of 0.25% compared with the other provinces [7]. Meanwhile, the prevalence of CKD patients in Yogyakarta was also included in the high prevalence group (0.3%) with East Nusa Tenggara, South Sulawesi, Lampung, West Java, Central Java and East Java [7].

3.2. Drug Combination and CAMs usage

Data of drug combination and CAMs usage in patients' especially chronic disease patients is essential to obtain a brief description on potential drug interactions. Table 1 list the number of drug combination in patients with CHF and CKD.

Table 1. Drug Combination in Patients

Drug combination	∑ CHF patients	∑ CKD patients	Total	Percentage (%)
≤ 3 combination	8	-	8	11
4 – 6 combination	21	29	50	68.5
> 6 combination	-	15	15	20.5
Total	29	44	73	100

As seen in Table 1, the majority of patients were being prescribed with 4 to 6 combination of drugs (68.5%). While drug combination could have beneficial effect on treating various diseases, the use of irrational drug combination (including CAMs) has been known to increase the risk of potential hazardous effect such as detrimental drug interactions [8]. Therefore rational drug combination should be a concern in healthcare providers in order to give the patient the optimum drug therapy.

Chronic kidney disease patients were identified with more drug combinations than CHF patients. This might occur because of various complications seen in patients with CKD such as anemia, electrolyte imbalance, osteodystrophy, etc whereas each complication has its own therapy [9]. This is different from CHF patients which usually are not accompanied with many complications. As for CAMs usage, Figure 2 describes the difference between the CHF and CKD patients.

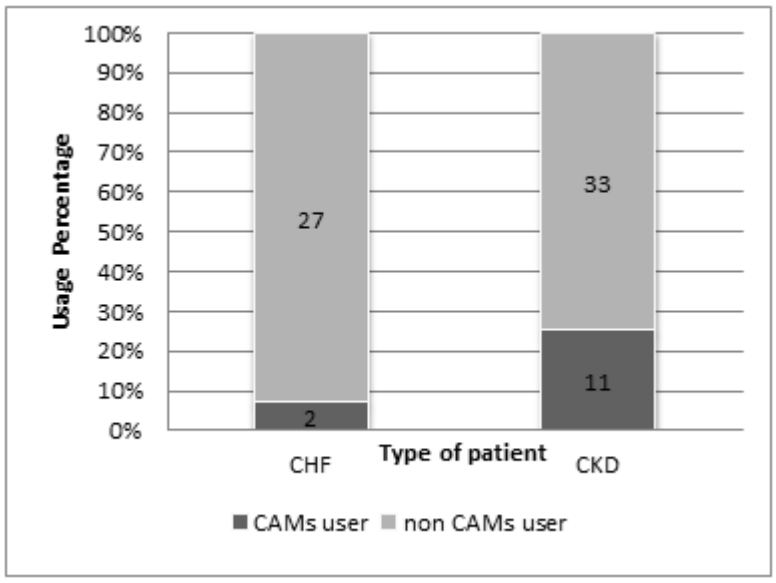

Figure 2. CAMs usage in CHF and CKD patients

Based on Figure 2, CKD patients were more familiar with CAMs usage compared with CHF patients (25% versus 6.9%). The high usage of CAMs in CKD patients in this study is similar with the results seen from a study in Thailand where half of the CKD patients included in the study used herbs and dietary supplements. These patients were mostly using herbs and supplements with a purpose of maintaining their well-being. Friends and family recommendation was the main reason to try, while perceived benefits of using the CAMs was mostly the reason to continue consuming them [10],[11].

3.3. Potential Drug Interaction

Potential drug interactions were identified by comparing drugs and/or CAMs consumed routinely with the new drugs prescribed by the doctor at the time of hospital visit. Drug interaction was then classified as pharmacokinetic and pharmacodynamic interaction based on the mechanism of the interactions.

Significancy of interaction as one of the important parameters in making follow up decisions was determined by classification from Tatro's Drug Interaction Facts (2010). The result can be seen in Table 2.

Table 2. Potential Drug Interactions in CHF and CKD patients

Drug A	Drug B	Interaction Mechanism		Significancy
		Ph. Kinetic	Ph. dynamic	
A. CHF patients				
Acetosal	Bisoprolol	1		4
Digoxin	Captopril	2		4
Digoxin	Lisinopril	5		4
Digoxin	Spironolakton	7		2
Furosemid	Digoxin		13	1
Furosemid	Captopril		2	3
Warfarin	Turmeric Acid		1	5
Clopidogrel	Fish Oil		1	2
B. CKD patients				
Acetosal	Vitamin B12	2		3
Acetaminophen	Furosemid	2		5
Nifedipine	Diltiazem	1		3
Omeprazole	Vitamin B12	2		5
Bisoprolol	Diltiazem	2		2
Bisoprolol	Clonidine		6	1
Furosemid	Captopril		5	3
Bisoprolol	Nifedipine		7	4
Acetosal	Captopril		1	2
Acetosal	Clopidogrel		1	1
Captopril	Epoetin Alpha		15	Unknown
Captopril	Potassium		1	Unknown
Captopril	Irbesartan		1	Unknown
Total of patients		24	54	
Percentage (%)		30.8	69.2	

Ph.kinetic: Pharmacokinetic, Ph.dynamic: Pharmacodynamic

As shown in Table 2, potential drug interactions identified in CHF and CKD patients mostly had pharmacodynamic mechanism. This type of interaction refers to drugs or substances that interact in the same receptor system, target of action or physiology system which then contributes to an additive (sinergistic) or antagonistic effect while pharmacokinetic interactions usually cause an increase or decrease of drug concentration in the blood eventually leading to toxic or subtherapeutic effect [12]. If compared with pharmacokinetic interactions, pharmacodynamic interactions usually needs a much deeper comprehension on the mechanism of action for the drugs or substance to interact [13]. Therefore predicting effect of this type of interactions may require several considerations.

When analyzing potential drug interactions in patients, consideration should be given mostly on types of interactions that are clinically significant which will possibly have significant effect on the patients. In this study, significance of the interaction can be seen by the number of significance level (last column in Table 2), where the smaller the number, the more significant. This should be the basis for healthcare provider (especially the pharmacist) to determine the best intervention in order to prevent detrimental effect on the patients due to drug interactions. The significance level of 1 indicates an interaction which is capable in causing permanent damage and death to patients [14]. Potential interactions identified in this level were furosemide with digoxin, bisoprolol with clonidine, and acetosal (aspirin) with clopidogrel. Given a high number of cases (13 cases), co-administration of furosemide with digoxin is a common prescription in CHF patients. Both drugs are essential to maintain CHF patient stability and has been recommended for heart failure patients with reduced ejection fraction [15]. The interaction between the two drugs is capable on increasing the risk of digoxin toxicity due to hypokalemia which can lead to effects such as arrhythmia. Many studies have shown digoxin toxicity leading to hospitalization among CHF patients prescribed with both digoxin and diuretic agents. A high incidence of hospitalization is mostly seen in CHF patients who receive more than one diuretic agent in combination with digoxin. Therefore combining digoxin with several diuretic agents must be avoided, while co-administration of digoxin with one diuretic agent such as furosemide can be handled by potassium monitoring (to determine risk of hypokalemia) and adding potassium supplement (to prevent hypokalemia) [14],[16].

Related to CAMs consumption in CHF and CKD patients, there were 2 cases (2.74%) of patients consuming turmeric acid and fish oil were identified with pharmacodynamics interaction with the other prescribed drugs. Turmeric acid has a potential interaction with warfarin which is an anticoagulant agent

usually prescribed in CHF patients with diagnose of atrial fibrillation in order to reduce the risk for thromboembolic event [17]. Turmeric acid is known to have an in vitro effect in the inhibition of platelet activating factor (PAF) and platelet aggregation therefore increasing the risk of bleeding in patients consuming anticoagulant. Documentation for this type of interaction has not yet been well established and there could be variation in pharmacological effect due to inconsistency of the herb potency itself [18]-[20]. A significance level of 5 for this potential interaction indicates a minor clinical significance; hence, the patient must still be monitored for risk of bleeding which is the most common side effect of warfarin. Awareness must be raised since warfarin is included in drugs with a narrow therapeutic index where risk of toxicity could increase or could become less effective if consumed with herbs [21].

While the potential interaction between turmeric acid and warfarin was stated as minor, another interaction with CAMs identified in this study had a significance level of 2. One patient prescribed with clopidogrel also consumed fish oil which (based on literature) could lead to an interaction between both. Fish oil is known to potentiate pharmacological effect of anticoagulant and other drugs which have effect on platelets and thrombin such as clopidogrel. Therefore this supplement has been widely used (and commonly prescribed by doctors) for patients with or at risk for cardiovascular diseases. A study of fish oil supplementation in diabetes patients using low dose aspirin shown that co-administration revealed a greater reduction of aggregation of platelet compared to aspirin alone. Despite the benefit of fish oil supplementation in patients also receiving antiplatelets or anticoagulants, consideration must be given specifically to patients with high risk of bleeding such as patients in plan for surgery or patients who appears with signs of even mild bleeding [22]-[24].

4. CONCLUSION

Complementary and alternative medicines (CAMs) usage was more familiar in CKD patients compared to CHF patients. Potential drug interactions with CAMs were identified (although in a small number; 2.74%) as pharmacodynamic mechanism through medication reconciliation process and should be taken into awareness by the healthcare team according to the significance level of interaction besides other prescribed drug interactions which are commonly seen in chronic disease patients.

ACKNOWLEDGEMENTS

We would like to thank Universitas Muhammadiyah Yogyakarta, Indonesia for the research grant given to complete this study.

REFERENCES

[1] F. Rahmawati, *et al.*, "Retrospective study of drug interactions in Dr. Sardjito hospital Yogyakarta," *Majalah Farmasi Indonesia*, vol/issue: 17(4), pp. 177–183, 2006.
[2] S. Supardi, *et al.*, "Use of manufactured traditional medicine for self medication in Indonesia," *Jurnal Bahan Alam Indonesia*, vol/issue: 2(4), pp. 136-41, 2003.
[3] S. Supardi and A. L. Susyanti, "Traditional medicine usage for self medication purpose in Indonesia: analysis of SUSENAS data year 2007," *Buletin Penelitian Kesehatan*; vol/issue: 38(2), pp. 80-89, 2010.
[4] H. H. Tsai, *et al.*, "Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review," *Int J Clin Pract*, vol/issue: 66(11), pp. 1056-1078, 2012.
[5] J. H. Barnsteiner, "Medication reconciliation" in R. G. Hughes, "Patient safety and quality: an evidence-based handbook for nurses, Rockville, MD, AHRQ Publication, vol. 2, 2008.
[6] B. H. Vaidhun and S. Amirthalingam, "Physicians expectations to prevent the drug interactions in clinical practice," *Int J Pharmacy and Pharm Sci*, vol/issue: 2(3), pp. 172-173, 2010.
[7] Indonesian Ministry of Health, "National primary health research," Jakarta, Badan Penelitian dan Pengembangan Kesehatan Indonesian Ministry of Health, 2013.
[8] H. C. Korting and M. S. Korting, "The benefit/risk ratio: a handbook for the rational use of potentially hazardous drugs," Florida, CRC Press, 2008.
[9] J. T. DiPiro, *et al.*, "Pharmacotherapy: a pathophysiologic approach, sixth edition," United States, The McGraw-Hill Companies, 2005.
[10] M. Tangkiatkumjai, *et al.*, "Prevalence of herbal and dietary supplement usage in Thai outpatients with chronic kidney disease: a cross-sectional survey," *BMC Complement Altern Med*, vol. 13, pp.153, 2013.
[11] M. Tangkiatkumjai, *et al.*, "Reasons why Thai patients with chronic kidney disease use or do not use herbal and diestary supplements," *BMC Complement Altern Med*, vol. 14, pp. 473, 2014.
[12] R. A. Helms and D. J. Quan, "Textbooks of therapeutics drug and disease management," Philadelphia, Lippincott Williams and Wilkins, 2006.
[13] Cascorbi I., "Drug interactions—principles, examples and clinical consequences," *Dtsch Arztebl Int*, vol/issue: 109(33–34), pp. 546–56, 2012.

[14] D. S. Tatro, "Drug interaction facts," Philadelphia, Lippincot William and Wilkins, 2006.
[15] C. W. Yancy, *et al.*, "ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," *J Am Coll Cardiol*, vol. 62, pp. e147–239, 2013.
[16] M. T. Wang, *et al.*, "Risk of digoxin intoxication in heart failure patients exposed to digoxin–diuretic interactions: a population-based study," *Br J Clin Pharmacol*, vol/issue: 70(2), pp. 258–267, 2010.
[17] R. O. *et al*., "ACC/AHA clinical performance measures for adults with systolic heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Heart Failure Clinical Performance Measures)," *J Am Coll Cardiol*, vol. 46, pp.1144–1178, 2005.
[18] W. Abebe, "Herbal medication: potential for adverse interactions with analgesic drugs," *J Clin Pharm Ther*, vol. 27, pp. 391–401, 2002.
[19] A. M. Heck, *et al.*, "Potential interactions between alternative therapies and warfarin," *Am J Health Syst Pharm*, vol. 57, pp. 1221-1227, 2000.
[20] X. Yang, *et al*., "Curcumin inhibits platelet-derived growth factor-stimulated vascular smooth muscle cell function and injury-induced neointima formation," *Arterioscler Thromb Vasc Biol*, vol. 26, pp.85–90, 2006.
[21] M. Y. M. Ismail, "Herb-drug interactions and patient counselling," *Int J Pharm Pharm Sci*, vol/issue: 7(2), pp. 1-7, 2009.
[22] R. C. Block, *et al*., "Effects of low-dose aspirin and fish oil on platelet function and nf-kappab in adults with diabetes mellitus," *Prostaglandins Leukot Essent Fatty Acids*, vol/issue: 89(1), pp. 9–18, 2013.
[23] P. M. K. Etherton, *et al.*, "Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease," *Circulation*, vol. 106, pp. 2747-2757, 2002.
[24] C. Alderman, "Antiplatelet effects of fish oil supplements," *RGH Pharmacy E-Bulletin*, vol/issue: 41(8), 2011.