NORA WULANDARI - POTENTIAL DRUG-DRUG INTERACTION AND ACTUAL ADVERSE EVENT IN HOSPITALIZED GERIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASES

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Potential Drug-Drug Interaction and Actual Adverse Event in Hospitalized Geriatric Patients with Chronic Kidney Disease

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Abstract. Chronic kidney disease (CKD) in Indonesia often occurs in elderly (geriatric) patients with various complications that cause polypharmacy which can increase the risk of drug-drug interactions (DDIs). This study aimed to determine the incidence of DDIs and actual adverse events in geriatric patients with CKD. This was a descriptive study where the samples were collected retrospectively from medical record of the patients admitted in one tertiary care hospital in Jakarta. Potential drug interaction was screened electronically using a drug interaction checker (drugs.com) and manually by Drug Interaction Fact 2014. A total of 699 potential DDIs were detected from 135 patients from one-year study period. The incidence of DDIs was 92.60% with 5.01% actual adverse event detected due to DDIs. Pharmacodynamic interactions accounted for 46.64% with the most significant level at a moderate level (59.37%). In conclusion, The prevalence of DDIs in geriatric patients with CKD was found high and major level of significance adverse event hyperkalemia was found caused by the DDIs.

Keywords: Drug interaction, Geriatric, Chronic kidney failure

1 Introduction

1. The elderly population is rising rapidly. Since 2015 the elderly population (60 years and older) in Asian including Indonesia increased by more than 7% [1]. Aging may alter physiological function increase the risk of communicable or non-communicable diseases. Four in every 100 elderly people are experiencing pain [2]. Ministry of the health of Indonesia reported that most of the geriatric inpatients (36.44%) stay in a hospital for a period of three days or less where 35.05% may have longer stay (4-7 days). Additionally, the ministry of health of Indonesia reported that 14.5% of elderly patients will remain in a hospital for treatment for a period longer than three weeks [1]. Among these last group of patients, complications due to Chronic Kidney disease (CKD) was one of the top ten cause of admission in r[2]dical elderly patients [2]. Chronic Kidney Disease (CKD) has a large global prevalence with steady estimated global CKD prevalence of more than 10 to 13% with mostly at stage 3 [3,4]. A study in Indonesia reported the incidences rate per million population of End Stage Renal Diseases (ESRD) who underwent hemodialysis and on hemodialysis from 2002 through 2006 were higher than 10 [5,6].

The management therapy [16]f CKD often involves multiple medications to get treatment goals purposed at slowing progression of CKD, treating complications and relieving symptoms. The management of CKD and co-morbidities makes polypharmacy a highly prevalent occasion in this population [7]. This makes drug-drug interactions (DDIs) often occur in patients. A study found polypharmacy in 74.9% of geriatric patients and within 91% patients had at least one potential DDIs [8].

DDIs is common in elderly. A study conducted in Yogyakarta-Indo[15]a showed out of the 100 cases of elderly patients, 65% cases had experienced potential DDIs range from 1 to 17 and of total 204 DDIs incidences, 25% were significance level [1]nd 39% of significance level 2 [9]. A study reported a total of 365 DDIs [1]re identified from 87 patients. Based on this study severity classification 244 (66.80%) moderate interactions were most common. Among the

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interaction 116 (31.70%) were of delayed onset and 74 (20.27%) were of rapid onset [10].

The DDIs that occur in patients has a possibility to generate adverse events (ADEs) in patients. A study showed 295 ADEs found in older adults among 20,628 visits of patients [11]. Another study reported older patients had the highest age-specific ADEs rate between 2005 and 2007 [12].

In regard to CKD, a study reported lisinopril and furosemide were the most frequent interaction prescribed drugs that were nephrotoxic affect serum potassium levels and implicated for DDIs [13]. The global economic impact of CKD is considerable to it requires a global effort to raise awareness of CKD, to incorporate prevention of CKD program in the public health agenda and to implement programs for early screening and detection of CKD [14]. Meanwhile, DDIs in geriatric with CKD in Indonesia especially in Jakarta is not well-documented. Therefore, the purpose of this study was conducted to determine the incidence of DDIs and actual adverse events in geriatric patients with CKD in one hospital in Jakarta.

2 Methodology

This was a descriptive which conducted in Islamic Hospital Jakarta Cempaka Putih. Data collection was taken from geriatric patients' hospitalization with CKD in 2017 which conducted retrospectively. The eligible inpatients were selected with inclusion criteria: age 60 or older, main diagnosed with CKD, and prescribed at least 2 drugs. Patients who were pregnant and died were excluded from this study. Drug profile containing herbal product or topical only including: creams, ointments, gels, patches, drops, sprays and inhalers were also excluded.

Potential drug interaction was screened electronically using a drug interaction checker which was accessed ugs.com and manually by Drug Interaction Fact 2014. Potential drug-drug interactions (DDIs) were grouped according to the mechanism, onset and the level of significance of the interaction. Meanwhile, the actual adverse event were checked retrospectively based on medical history of the patients.

This study was approved by the Universitas Muhammadiyah Prof DR. HAMKA Ethics Committee (01/18.09/034).

3 Result and Discussion

During 2017 there were 426 hospitalized patients with CKD. Two hundred and ninety-one of the patients were excluded because of died during the treatment (198 patients) and incomplete medical record such as laboratory information in their medical record (93 patients). So the final samples in this study were 135 patients.

3.1 Characteristics

Socio-demographic characteristics, the patients in this study were mostly male with classification age 60-75 year. In regard to clinical characteristics, patients in this study mostly had a length of stay 3-5 days with number recipes 3-5 and number of drugs 5-8 items. These characteristics can be seen in Table 1.

Table 1. Patients' socio-demographic and clinical characteristics

Characteristic	*n*	%
Gender		
Male	72	53.3
Female	63	46.7
Age (year)		
60-75	74	54.8
76-90	61	45.2
Length of stay (day)		
3-5	101	74.8
6-8	34	25.2
Number of recipes		
3-5	101	74.8
6-8	34	25.2
Number of drugs		
5- 8 9-12	95 40	70.4 29.6

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The overview of drug interactions is shown in Table 2. The percentage of potential DDIs showed that almost all geriatric patients got regimen of drugs.

Table 2. Overview Potential DDIs

Characteristic DDIs	*n*	%
Patients who had the potential DDIs	125	92.6
Patients who did not have the potential DDIs	10	7.4
Total	135	100
Mechanism of DDIs		
Pharmacokinetic	317	45.35
Pharmacodynamic	326	46.64
Unknown	56	8.01
Total	699	100
Onset of DDIs :		
Rapid	31	4.43
Delayed	184	26.32
Unknown	484	69.25
Total	699	100
Level of Significance :		
Major	74	10.59
Moderate	415	59.37
Minor	210	30.04
Total	699	100

Based on its mechanism, the DDIs are divided into pharmacokinetic interactions, pharmacodynamic interactions. These type of mechanisms can be seen in all patients who had potential drug interactions. Among 135 patients, 699 potential DDIs were identified. Pharmacodynamic and pharmacokinetic DDIs were most common constituting 46.64% and 45.35%, respectively. Meanwhile, the other 8.01% were unknown.

The most common pharmacodynamic interactions are interactions between Amlodipine and calcium carbonate ($CaCO_3$) as many as 45 (13.50%) occurrences of interactions. This similar to another study which showed calcium carbonate and amlodipine were most common potential DDIs in CKD with 114 times frequency [15]. The combination use of the two drugs can make effects of amlodipine declined. The recommendation to this case may need a dose adjustment of blood pressure monitoring [16].

The most common pharmacokinetic interactions were between Ranitidine and $CaCO_3$ interactions as many as 35 (11.04%) occurrences of interactions. Oral antacids which consist of for instance calcium salts may reduce the plasma concentration of oral H2 blockers. The recommendation in this case is H2 blockers should be given one to two hours before one of these preparations [16]. Reduction gastric absorption and bioavailability ranitidine occur because of the neutralizing effect of antacid (calcium salt) was suspected mechanism [17]

In this study, the most common rapid onset of drug interactions was between aspirin and nitroglycerin with 15 (48.39%) interactions. The administration of aspirin reported can increase the antihypertensive effect of nitroglycerin. This mechanism is unknown but might be related to the prostaglandin system. Though this is minor interaction, the management monitoring blood pressure during co-administration may be considered [16].

The most common delayed-onset drug interactions were between aspirin and furosemide as many as 23 (12.5%) interaction events. This interaction occurs as a result of prostaglandin inhibition resulting from aspirin use, which disrupts the effects of furosemide [16].

In this study, the most major interactions were between omeprazole and clopidogrel, which occurred in 14 (18.92%) interactions. Co-administration with proton pump inhibitors (PPIs) may reduce the cardioprotective effect of clopidogrel [16]. Clopidogrel needs bioactivation by cytochrome P450 2C19 in the liver in order to exert its inhibitory effect on platelet aggregation, while competitive inhibition of this isoenzyme by PPIs impair activation of clopidogrel [18,19].

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Among the 699 potential DDIs, 21 times the actual adverse event was found which can be seen in **Table 3**. There were three kinds of actual adverse event that found in this study, i.e hyperkalemia, hypomagnesemia and increased hypokalaemia.

Table 3. Actual Adverse event from DDIs

No	Actual adverse event	Name of drugs	*n*	%
1.	Hyperkalaemia	Spironolactone - KCL	2	9.52
		Spironolactone-Candesartan	2	9.52
		Spironolactone-Telmisartan	3	14.29
		Spironolactone-Captopril	1	4.76
		Captopril – KCL	1	4.76
2.	Hypomagnesemia	Furosemide-Omeprazole	6	28.57
		Furosemide – Lansoprazole	3	14.29
3.	Hypomagnesemia and/or Hypocalcemia	Furosemide – Digoxin	3	14.29
Total			21	100

Hypomagnesemia caused by furosemide-omeprazole were the most common actual adverse event (28.57%), while the other proton pump inhibitor (PPIs) lansoprazole was also causing the effect in concomitant with furosemide (14.29%). This was a moderate level of significance DDI. Patients found to experienced hypomagnesemia with plasma magnesium from 1.5 to 1.7 after 1 to 5 days co-administration of the drugs. Hypomagnesemia may occur during long-term combination PPIs and diuretic. Hypomagnesemia can occur during long-term PPI use is unknown, although changes in magnesium intestinal absorption may be seen. The recommendation in this case is monitoring of serum magnesium levels periodically before and after starting therapy [16,20]. A study conducted among hemodialysis patients to investigate the relationship between PPIs use and hypomagnesemia found that furosemide use is a risk factor for hypomagnesemia [21].

The major significance level of DDIs which were between spironolactone and KCL, candesartan, telmisartan, captopril as well as between captopril and KCL found to cause actual hyperkalemia with range plasma potassium level from 5.2 to 6 mEq/L. The patients experienced hyperkalema after 1 to 6 days after the combination drugs administration. Potassium sparing agent and potassium itself in KCL will increase the plasma potassium level. The use of angiotensin converting enzyme inhibitor (ACEIs) such as captopril or angiotensin II receptor blockers (ARBs) such as losartan, candesartan, telmisartan caused in decreased aldosterone, which can cause potassium retention. As a results, hyperkalemia often happened in pasien who using the concomitant of the drugs [16].

Meanwhile there were 3 case of actual drug event which found in moderate DDIs between furosemide and digoxin. Three patients found to have hypokalemia and/or hypomagnesemia with plasma potassium level 3.2-3.4 mEq/L and/or plasma magnesium level around 1.5 -1.7 mEq/L after 1 to 3 days after got the combination drugs. The mechanism hypomagmesemia induced by proton pump inhibitors (PPIs) is still unknown, although it has been reported that there is a change in intestinal absorption of magnesium. There has been reports that hypomagnesemia associated with long-term use of PPIs [20,22]. Hypomagnesemia can also cause disturbed secretion of parathyroid hormone which may cause hypocalcemia [16].

Conclusion

The prevalence of DDIs in geriatric patients with CKD was found high and major level of significance adverse event hyperkalemia was found caused by the DDIs. The most common DDIs with major significance level and frequently generate the actual adverse event in geriatric patients need to be watched out by clinicians. The critical role of the clinical pharmacy lies in detection, prevention, and management of DDIs and actual adverse events so that the goal of improvement of therapeutic outcomes can be achieved.

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