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Research Article

POTENTIALITY OF DRUG-DRUG INTERACTIONS IN HOSPITALIZED GERIATRIC PATIENTS IN A PRIVATE HOSPITAL, YOGYAKARTA, INDONESIA

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ABSTRACT

The increasing number of drugs available and the increasing use of multidrug regimens in elderly patients enhance the possibility for drug interactions. The aim of the study was to determine the occurrence of potential drug-drug interactions (DDIs) and the association between the number of drugs and DDIs. Research type was observational. Data was obtained retrospectively, taken from 100 cases of geriatric patients' hospitalization medical records in a private hospital at Yogyakarta in Indonesia from July until December 2007. The finding of this study showed that the mean number of medication per cases per day was $5.8 \pm 2.1 (\pm SD)$. Of the 100 cases, 65% cases had experienced potential DDIs range from 1 to 17. Of total 204 DDIs incidences, 25% were of significance level 1 and 39% of significance level 2. Twelve cases (12 %) have more than 4 incidences of DDIs. Our study showed that the number of potential DDIs increased as the number of medications used per day increased. Geriatric patients taking nine or more medication tended to have more DDIs (6.8 ± 5.5) in comparison to those with one to two medications with no DDIs. The result of linear regression analysis indicated that number of medication used per day have positive relationship on number of DDIs (p=0.000). Incidence of DDIs in geriatric patients was frequent and pharmacist can play a critical role in managing medication therapy of patients with collaboration with other professional health care to prevent adverse drug reactions.

Key words: Drug-drug interaction, Geriatric patient, Drug safety.

INTRODUCTION

Indonesia's population is ageing rapidly; it is predicted to have the tenth largest elderly population in the world. The number of persons aged 60 years and over per 1000, was estimated at 54/1000 in 1980 and 76/1000 in 2000. It is projected that the proportion of the elderly will reach about 9.8% of the total population in 2010. With such an increase in the absolute number of the elderly in Indonesia, this age group will reach almost 28 million within the next few years (2020). The growth rate of the elderly population will be 3.7% between 2010 and 2020, compared with a population growth rate of 0.8% ¹.

The rapidly growing numbers and proportion of elderly mean that more people will be entering a period of life where the risk of developing chronic degenerative diseases and debilitating diseases are significantly higher. Then, people over the age of 65 years are more likely to be on medication than younger people. They will often take several drugs to treat concomitant disease processes ^{2, 3}.

In elderly, concomitant use of several drugs (polypharmacy) is very common, and carries a high risk of both drug-drug interactions and drug-disease interactions ^{4, 5}. In nursing home resident, the prevalence of potential DDIs was 25 % ⁶. Previous study found relationship between number of medication and potentially severe DDIs ⁷.

Multiple diseases prompt multiple drug use in the elderly, raising the risk of drug interactions. Several type of drug interactions exist: drug-drug, drug-disease, drug-food, drug-alcohol, drug-herbal products and drug-nutritional status. A drug-drug interaction can be defined as the effect that one drug has on another. Drug-drug interactions can be pharmacokinetic or pharmacodynamic in nature. The outcome is an amplification or decrease in the therapeutic effects or side–effects of a specific drug ⁸. Some hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions such as hypoglycemia after patients receiving glyburide concurrent with co-trimoxazole, digoxin toxicity (digoxin with clarithromycin), and hyperkalemia after being treated with ACE inhibitors and potassium sparing diuretic⁹. A study reported that 13% of preventable prescribing errors detected in ambulatory patients involved drug interactions ¹³.

In spite of this evidence, however little information is available about the prevalence of DDIs in geriatric hospitalized in developing country, because many studies have been done in developed country. The aim of the study was to determine the occurrence of drug-drug interactions (DDIs) and the association between the numbers of drugs used per day during hospitalization with the number of potential DDIs.

METHODS

Design and data collection

Research type was descriptive observational. Data collection was conducted retrospectively, taken from 100 cases of geriatric patients' hospitalization medical records in a private hospital, Yogyakarta, Indonesia. We collected the data through reviewing medical record with inclusion criteria: patient 65 year and above, complete medical record, patient hospitalized for two days and more, and patient admitted to hospital from the period beginning July until December 2007 in the internal medicine department.

The variables analyzed were general characteristics of the patient (gender, age), current medical history (diagnosis), and medicines prescribed during hospitalization. The medication use of geriatric patients during hospitalization was recorded in Exel. Then, the medication were classified and encoded according to MIMS Indonesia 105th Ed. To look for potential interactions every combination of prescribed drugs was analyzed by using the drug-drug interactions software Facts & Comparisons programs. DDIs were defined as two medications that coincided.

The matching results of DDIs were classified into five categories (significance level one to five). In this classification, drug interactions are at significance level one when interaction categories are divided into potentially severe or life-threatening interaction; occurrence has been suspected, established or probable in well controlled studies; contraindicated drug combinations may also have this number. One interaction at significance level two can cause deterioration in a patient's clinical status; occurrence suspected, established or probable in well controlled studies. A potential drugdrug interaction at significance level three presents a potential for minor effects; occurrence suspected, established or probable in well controlled studies. While drug-drug interaction at significance level four might cause moderate-to-major effects; but data is very limited. Then, drug interaction at significance level five may cause minor-tomajor effects; occurrence is unlikely or there is not good evidence of an altered clinical effect.

Variables	Number of cases	%
Gender		
Female	46	46.0
Age group (years)		
65-69	16	16.0
70-74	32	32.0
75-79	29	29.9
> 79	23	23.0
The 7 most common diagnosis of hospitalized geriatric patients		
Cardiovascular disease	30	30.0
Infection disease	22	22.0
Respiratory disease	20	20.0
Gastrointestinal disorder	20	20.0
Cerebrovascular disease	18	18.0
Endocrine disorder	14	14.0
Cancer	7	7.0
Distribution of the number of medications prescribed among hospitalized geriatric patients		
Drugs for cardiovascular and hematopoeietic system	228	22.8
Neuro-muscular drugs	176	17.6
Drugs for gastrointestinal and hepatobiliary	175	17.5
Antibiotics	139	13.9
Drugs for respiratory system	122	12.2
Vitamins and minerals	81	8.1
Drugs for endocrine and metabolic system	36	3.6
Corticosteroid hormones	23	2.3
Drugs for allergy and immune system	10	1.0
Drugs for genito-urinary system	7	0.7
Other chemotherapeutics	3	0.3
The number of medication prescribed during hospitalization		
< 5	13	13.0
5 – 10	48	48.0
> 10	39	39.0

Statistical analysis

All collected data regarding medications prescribed were included in the analysis. The descriptive analysis included absolute and relative frequencies of categorical variables. SPSS 11.5 was used to run statistical analysis. Linear regression was used to predict the relationship between the number of drugs and drug-drug interactions (DDIs).

RESULTS AND DISCUSSION

General characteristic

Of the 100 cases of hospitalized geriatric patients, 46 cases (61.3%) were women. Their ages range from 66 to 97 years, with the average age was 75.1 ± 5.8 (\pm SD). Majority of patients' ages were between 70-74 years old. Yogyakarta province has the highest proportion of older population (13.72%) in Indonesia. The statistical data related with life expectancy for elderly in Yogyakarta, were 72 years old for women and 69 years old for men¹⁰. The characteristics of geriatric patients hospitalized are shown in Table 1.

Our study showed the most common disease in geriatric hospitalized were cardiovascular and infection disease. According to a survey from Household Health Survey Indonesia in year 1995, the three major diseases affecting older persons were: circulatory disease (29.5%), respiratory disease (12.2%), and cancer (12.2%)¹.

A report from more and Romsdal Prescription Study (MRPS) in Norwegian county mentioned the cardiovascular diagnoses were the highest incidence in their study¹¹.

As expected, cardiovascular system drugs were the most frequently prescribed (22.8%), followed by neuro-muscular drugs (17.6%), drugs for gastrointestinal and hepatobiliary (17.5%), anti-infectives (13.9%) and drugs for respiratory system (12.2%). These were the five most widely dispensed therapeutic groups. Many studies have documented the most commonly prescribed class of medications used by elderly patients was cardiovascular system drugs ^{67,11}.

In this study, medication use range during hospitalization was three (3) until twenty six (26) different medications. Eighty seven (87) patients received more than 5 medications during hospitalization. A

lot of medication used might cause symptoms and patient's diagnosis often changes during hospitalization and it involves a lot of diagnosis in elderly patients.

Occurrence of DDIs

Elderly people receive a higher number of prescriptions in hospital and in the community. The findings of this study showed that the mean number of medication per cases per day was $5.8 \pm 2.0 \ (\pm SD)$. Of the 100 cases, 65% had experienced drug-drug interactions (DDIs) with range from 1 to 17 DDIs. Twelve cases (12 %) have more than 4 incidences of DDIs (Table 2). Previous study found the prevalence of potential DDIs range from 25.1 to 79%, but the figures vary greatly in relation to the setting, population and system of DDIs evaluation $^{4.6.7}$.

Table 2: Frequency of drug-drug interactions of the		
medications of sampled cases		

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Frequency of drug-drug interactions	Number of cases	%			
No drug interaction	35	35.0			
1	22	22.0			
2	14	14.0			
3	9	9.0			
4	8	8.0			
5	4	4.0			
6	1	1.0			
7	3	3.0			
9	1	1.0			
11	2	2.0			
17	1	1.0			
Total	100	100.0			

The ten active substances most frequently involve in potentially DDIs are shown in Figure 1. Several cardiovascular drugs were the most frequently involved (low dose acetylsalicylic acid, furosemid, spironolactone), followed by neuro-muscular drugs (diazepam, phenobarbital), drugs for gastrointestinal (ranitidine, omeprazole) and respiratory system drugs (aminophylline, theophylline).Elderly patients are the population at the highest risk of potential DDIs. They frequently take many drugs (polypharmacy), have several co-

morbidities, and might not maintain adequate nutritional status. The application of evidence-based medicine tends to increase the number of drugs prescribed to treat one disorder. Additionally, agerelated changes in pharmacokinetics and pharmacodynamic characteristics included impairment in many organ functions (particularly kidney and liver) that increase the complexity of drug interactions in elderly people ⁸.



Figure 1: Active substances most frequently involved in potential drug interactions

Of total 204 DDIs incidences, 25 (12.5 %) were of significance level 1 and 39 (19.1%) of significance level 2 (Table 3). The importance of drug interactions in clinical practice primarily involves knowing or predicting those occasions when a potential interaction is likely to have significant consequences for the patient. When these arise, health professional should take step to minimize adverse effects, for example by using an alternative treatment to avoid the combination risk, by making a dosage adjustment, or by monitoring the patient closely. In order to predict the possible consequences of the administration of two or more drugs it is essential that the health professional has a practical knowledge of the pharmacological mechanism involved in drug interactions, an awareness of the drugs associated with great risk, and the most susceptible patient group ¹².

Table 3: Frequency of different significance levels of DDIs			
Level of significance	Frequency	%	
1	25	12.3	
2	39	19.1	
3	28	13.7	
4	20	9.8	
5	92	45.1	
Total	204	100.0	

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The findings also showed that the number of potential DDIs tend to increase as the number of medications used per day increased. Geriatric patients with nine or more medication tended to have more DDIs (6.8 ± 5.5) in comparison to those with one to two medications with no DDIs (Table 4).

Table 4: The number of consumed drug vs absence of notential DDIs

potential DD15		
Number of medications used	Number of potential DDIs	
per day	(mean ± SD)	
1-2	0	
3-4	0.72 ±1.22	
5-6	1.51 ± 1.58	
7-8	3.45 ± 2.82	
9-10	6.86 ± 5.49	

A recent study showed a strong relationship between number of drug and the potential of DDIs ^{6, 7}. To further identify how the number of medication influenced DDIs, our study used linear regression to estimate the influence of number of medication used per day on number of DDIs. The independent variables were number of medication used per day, while the dependent variables were number of DDIs. The result of linear regression analysis indicated that number of medication used per day have positive relationship

on number of DDIs with equation Y = 0.363x - 1.594. R Square = 0.313 mean not only number of medication that have contributed to the increase number of DDIs but also several factors such as type of medication use might contribute to increase number of DDIs. In addition p = 0.000, suggesting the model's estimate was fit to the data at an acceptance level.

The potential DDIs are common in the elderly patients during hospitalization. Professional health care should be aware with elderly patients, especially those being treated with polypharmacy for chronic disease, those taking drugs with a narrow therapeutic index, and drugs metabolized by enzymes susceptible to induction or inhibition. This is because they have the highest of DDIs. Results from a meta-analysis showed that elderly patients usually do better when their care is managed by a multidisciplinary team consisting of a physician (geriatrician), nurse, and pharmacist. Communication between these professionals is crucial for success. By combining their knowledge and skills, a comprehensive plan can be developed to enable best pharmacotherapy while the risks of drug interactions are reduced ¹⁴.

CONCLUSION

Incidence of potential DDIs in hospitalized geriatric patients in Indonesian hospital was substantial. To reduce potential DDIs, the number of medications for the geriatric patients should be properly controlled and it is recommended to eliminate all medications without therapeutic benefit, goal or indication. Beside, pharmacist should increase their role in managing medication therapy through collaboration with other professional health care to prevent and resolve drug-drug interaction problem.

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