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Original Article

DRUG-RELATED PROBLEMS IN CHRONIC KIDNEYS DISEASE PATIENTS IN AN INDONESIAN HOSPITAL: DO THE PROBLEMS REALLY MATTER?

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ABSTRACT

Objective: To identify and evaluate drug-related problems (DRPs) in patients with chronic kidney disease (CKD).

Methods: A prospective observational three-month study was conducted in adult patients with CKD hospitalised in five general medical wards and one intensive cardiac care unit in a major teaching hospital in Indonesia. Principal researcher (pharmacist) identified the occurrence of DRPs through the direct patient interview, discussion with nurses and assessment of patients' medication charts and medical records. The identified DRPs were validated by a senior pharmacist and classified using Pharmaceutical Care Network Europe/PCNE classification scheme for DRP V6.2. Descriptive analysis was applied for demographic data, drug utilization and DRP profiles.

Results: There were 105 patients who met the inclusion criteria and 80% of these patients had end-stage renal disease. A total of 2404 medication orders were reviewed and 1026 DRPs were identified. Potential DRPs accounted for around two-thirds of the cases. The rate of overall DRPs was 42.7 DRPs per 100 medication orders and each patient in the study experienced approximately ten DRPs during their hospitalization. Treatment effectiveness and adverse reaction domains contributed to the majority of DRPs primary domains for problems. Drugs for cardiovascular diseases and drugs for correcting electrolyte imbalance were most commonly implicated in DRP incidence.

Conclusion: This study uncovered higher rate of DRPs experienced by each patient compared to other CKD studies. There were variations of DRP types when comparing with similar studies. Pharmacists' competencies to identify, prevent and resolve DRPs are vital measures to improve clinical outcomes in CKD patients.

Keywords: Drug-related problems, Chronic kidney disease, PCNE classification

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INTRODUCTION

Kidney disease is one of global health problems requiring early detection and treatment to prevent its progression [1]. In accordance to reports from World Health Organization (WHO), genitourinary diseases including kidney disease contributed to more than 26 million disability-adjusted life years [2] and were responsible for approximately 800,000 mortality cases each year worldwide [3]. In the United States, the prevalence of end-stage kidney disease was estimated around 1,665 per million population [4], whilst it was reported to be 822 per million population in Australia [5]. In addition, the prevalence of patients receiving renal replacement therapies in European countries ranged between 421-1,152/million population [6]. In Indonesia, kidney diseases accounted for top five diseases leading to hospitalization and death [7]. Further, kidney disease-related health care costs predominantly burden national health insurance expenses particularly the direct costs attributed to renal replacement therapies (i.e. hemodialysis) for treating chronic kidney disease [8].

Chronic kidney disease (CKD) is characterised by the decline of kidney function within long period [9]. The decline of kidney function causes a range of complications including metabolic abnormalities, endocrine complications and increased risk of cardiovascular diseases. These complications, if not managed appropriately, may implicate on the prolonged length of stay in the hospital and increased mortality rate [10]. Further, CKD was associated with alteration in the pharmacokinetics of a range of drugs in particular renal-excreted drugs. The pharmacokinetic alterations may include the changes in drug bioavailability, protein binding level, drug distribution and elimination. Unfortunately, this condition will make patients become vulnerable to drug-related problems (DRPs). In addition, the progression of CKD may lead to the increased number of medications taken by patients to manage the complications and the comorbidities, and subsequently increase the prevalence of DRPs [11, 12].

DRP is defined as "an event occurring, as a result, the drug therapy that actually or potentially interferes with desired health outcomes"[13]. It has been evident that the occurrence of DRPs may result in significant morbidity and decrease patients' health-related quality of life in varied clinical settings. In relation to CKD, a range of studies have reported that DRP cases are considerably prevalent and attributed to significant implications [14-17]. Therefore, thorough knowledge of DRPs may benefit health care professionals including pharmacists to identify DRPs, resolve actual DRPs and prevent potential DRPs in order to optimise patients' outcomes. Nonetheless, it is quite unfortunate that limited prospective studies on evaluation of DRPs in patients with chronic kidney diseases have been conducted in Indonesian hospitals. Thus, this study aimed to identify and evaluate drug-related problems (DRPs) in patients with chronic kidney diseases

MATERIALS AND METHODS

A prospective observational three-month study was conducted in adult patients (18 y or older) who were diagnosed with chronic kidney disease at all stages and hospitalised in five general medical wards and one intensive cardiac care unit in a major teaching hospital in Indonesia. The study protocol was approved by Faculty of Pharmacy Pancasila University Institutional Review Board and Human Ethics Committee at the study hospital (Approval No: DM.03.01/II.3/2226). The patients observed in the study received information sheet prior to consenting to participate.

Data collection was conducted during patient hospitalisation and discharge time. Data collected included date of admission/discharge, patients' socio-demographic data (age, sex, weight, height, type of insurance, smoking status, alcohol/substance abuse, dietary and exercise pattern), comorbidities/past medical history, past

medication history (including herbal medicines and over-the-counter medicines), allergy/adverse drug reaction history, current medication profiles, discharge medications, laboratory investigations, physical and diagnostic examinations.

Principal researcher (pharmacist) identified the occurrence of DRPs through the direct patient interview, discussion with nurses and assessment of patients' medication charts and medical records. The identified DRPs were validated by a senior pharmacist and classified using Pharmaceutical Care Network Europe/PCNE classification scheme for drug-related problems V6.2 [18]. According to PCNE DRP classification scheme, DRPs were categorised into four primary domains for DRP problems and eight primary domains for DRP causes. The medications prescribed and involved in the DRPs were categorised using Indonesian National Formulary. The rate of DRPs was defined as the rate of DRPs per 100 medication orders and the number of DRPs per each patient. Further, DRPs were divided into actual and potential DRPs.

Demographic data, drug utilisation and DRP profiles were summarised using descriptive statistics (mean±standard deviation or median [range] for variables measured on a continuous scale, and frequencies and percentages for categorical variables). Descriptive statistical analysis was carried out using the SPSS® version 22.0 statistical package.

RESULTS

Demographic characteristics and patients' comorbidities

There were 105 patients who met the inclusion criteria over the three-month study and the demographic characteristics are summarised in table 1. On average the patients aged approximately 50 y and there were slightly more female patients. As seen in table 1, all patients in the present study relied on insurance to cover their health-related expenses where nearly all (94.3%) were the holder of the national insurance scheme. In addition, the majority of patients (80.0%) had CKD-V stage with glomerular filtration rate/GFR less than 15 ml/min/1.73 $m^2$and more than half received hemodialysis. The data also uncovered nearly 90% of patients were hospitalised once during the study period and there were notable variations in the length of stay with the average duration of hospitalisation was 15 d. In regards, the prevalence of co-morbidities, more than half of the patients had 6-10 other chronic diseases and the most common co-morbid conditions including hypertension, diabetes mellitus, ischemic heart diseases, heart failure and cerebrovascular diseases.

Profile of drug utilisation and DRPs

There were 2404 medication orders for CKD patients during the study period (table 2). Generic drugs (53.3%) were prescribed slightly more frequent than their counterparts. As outlined in table 2, cardiovascular drugs accounted for the most common drug classes prescribed, followed by fluid and electrolytes, and drugs for gastrointestinal system. Further, the ten most prevalent drugs prescribed in the study setting included amlodipine, sodium bicarbonate, omeprazole, ceftriaxone, folic acid, vitamin B12, insulin, furosemide, n-acetylcysteine and paracetamol. Our data also uncovered that almost 60% of patients took 6-10 drugs per day, one-third of patients were prescribed more than 10 drugs/day patients leaving just 3.8% of patients taking less than five drugs/day.

Table 1: Patients' demographic characteristics during the study period (N=105)

Variable	Category	N (%)
Age (years)	15-44	30 (28.6)
	45-64	66 (62.9)
	≥65	9 (8.6)
Sex	Male	48 (45.7)
	Female	57 (54.3)
Body Mass Index	Underweight	12 (11.4)
	Normal	64 (60.9)
	Overweight	22 (20.9)
	Obesity	7 (6.7)
Payer	National Health Insurance	99 (94.3)
	Private Insurance	6 (5.7)
CKD stage (according to KDIGO)	G3b. Moderately to severely decreased (GFR 30-<45 ml/min/1.73m^2)	5 (4.8)
	G4. Severely decreased (GFR 15-<30 ml/min/1.73m^2)	16 (15.2)
	G5. Kidney Failure (GFR<15 ml/menit/1.73m^2)	84 (80.0)
Receiving hemodialysis	Yes	62 (59.0)
	No	43 (41.0)
Hospitalization	1x	93 (88.6)
	2x	9 (8.6)
	3x	3 (2.9)
Length of Stay (days)	≤14	52 (49.5)
	15-28	40 (38.1)
	>28	13 (12.4)
Presence of co-morbidities	<5	12 (11.4)
	6-10	60 (57.1)
	11-15	28 (26.7)
	>15	5 (4.8)

eGFR = estimated glomerulus filtration rate, KDIGO = Kidney Disease: Improving Global Outcomes, n = number of observed patients who met the inclusion criteria (i.e. 105 patients)

A total of 1026 DRP cases were identified, and potential DRPs accounted for around two-thirds of the cases. The rate of overall DRPs was 42.7 DRPs per 100 medication orders. On average, each patient in the study experienced ten DRPs during their hospitalisation. DRP profiles with problems as primary domains identified by the principal researcher are presented in table 3. As depicted in table 3, both treatment effectiveness and adverse reaction domains contributed to the majority of DRPs with a similar proportion, whilst domain of treatment costs comprised around 7% of all DRPs. When conducting further analysis of DRP sub-domains, DRPs related to non-allergic adverse drug events (38.9%) and sub-optimal effect of drug treatment (28.7%) were identified as the two major DRP problems. Most cases of non-allergic adverse drug events were attributed to gastrointestinal bleeding/upset, potassium imbalance and diarrhea. The three major drugs responsible for the non-allergic events were anti-platelets (aspirin, clopidogrel), phosphate binders and laxatives. Meanwhile,

sub-optimal effect of drug treatment occurred mainly due to the presence of drug-drug interactions and drug-food interactions (n=131, 12.8%), drugs not taken/administered (n=81, 7.9%) and untreated indication (n=71, 6.9%) which mostly involved the use of anti-hypertensives (captopril, amlodipine) and calcium carbonate. In addition, the domain of treatment cost was associated with extra costs due to unnecessary treatment with domperidone and paracetamol as the most implicated drugs.

Table 2: Drug classes of medications (n=2404) prescribed for chronic kidney patients

Therapeutic classes	N (%)
Cardiovascular drugs	417 (17.4)
Fluid, electrolytes and parenteral nutrition	380 (15.8)
Gastrointestinal drugs	284 (11.8)
Anti-infectives	213(8.9)
Drugs acting on the Blood or Blood Forming Organ	206 (8.6)
Vitamins and Minerals	180 (7.5)
Hormones, endocrine drugs and contraceptives	170 (7.1)
Diuretics and prostate drug	159 (6.7)
Respiratory drugs	144 (5.9)
Analgesic, antipyretic, NSAID and anti-gout agent	123 (5.1)
Others	128 (5.3)

N= number of medication orders during the study (i.e. 2404 medication orders)

Table 4 outlines DRP profiles with causes as primary domains. The selection of drug was the most prevalent cause of DRPs identified by the pharmacist. This domain constituted nearly two-thirds of all DRPs. Further, dose selection was responsible for 37.7% of DRP cases, followed by drug use process (20.9%) and logistics (14.4%). When analysing DRP sub-domain, there were five major DRP causes included inappropriate combination (41.8%), pharmacokinetic problem (14.3%), drugs not taken/administered (12.6%), dosage regimen too frequent (9.3%) and prescribed drug not available (8.1%), respectively.

Table 3: The Frequency of drug-related problem/DRP (Primary domains for problems), N=1026

DRP Domain	DRP sub-domain	Actual DRP	Potential DRP	Total (%)
Problem 1	P1.1 No effect of drug treatment	87	14	101(9.8)
(Treatment effectiveness)	P1.2 Effect of drug treatment not optimal	74	220	294 (28.7)
	P1.3 Wrong effect of drug treatment	0	0	0
	P1.4 Untreated indication	88	0	88 (8.6)
Total		249	234	483 (47.1%)
Problem 2	P2.1 Adverse drug event (non-allergic)	30	370	400 (38.9)
(Adverse reactions)	P2.2 Adverse drug event (allergic)	0	6	6 (0.6)
	P2.3 Toxic adverse drug event	1	69	70(6.8)
Total		31	445	476 (46.4%)
Problem 3	P3.1 Drug treatment more costly than necessary	32	1	33(3.2)
(Treatment costs)	P3.2 Unnecessary drug treatment	35	0	35(3.4)
Total		66	1	67 (6.5)

N = Total number of drug-related problems identified (i.e. 1026 drug-related problems)

Table 4: The frequency of drug-related Problem/DRP with causes as primary domains, N=1026

DRP domain	DRP sub-domain	Actual DRP	Potential DRP	Total (%)
Cause 1	C1.1 Inappropriate drug	24	32	56 (5.5)
Drug selection	C1.2 No indication for drug	32	3	35 (3.4)
	C1.3 Inappropriate combination	32	397	429 (41.8)
	C1.4 Inappropriate duplication.	14	18	32 (3.1)
	C1.5 Unnoticed indication	73	0	73 (7.1)
	C1.6 Too many drugs for indication	10	4	14 (1.4)
	C1.7 More cost-effective drug available	0	0	0
	C1.8 Synergetic or preventive drug required	24	1	25 (2.4)
	C1.9 New indication presented	18	0	18 (1.8)
Total		227	455	682 (66.5)
Cause 2 Drug form	C2.1 Inappropriate drug form	0	2	2 (0.2)
Total		0	2	2 (0.2)
Cause 3	C3.1 Drug dose too low	10	22	32 (3.1)
Dose selection	C3.2 Drug dose too high	2	68	70 (6.8)
	C3.3 Dosage regimen not frequent enough	0	3	3 (0.3)
	C3.4 Dosage regimen too frequent	3	92	95 (9.3)
	C3.5 No therapeutic drug monitoring	0	18	18 (1.8)
	C3.6 Pharmacokinetic problem	2	145	147 (14.3)
	C3.7 Deterioration/improvement of disease	17	5	22 (2.1)
Total		34	353	387 (37.7)
Cause 4	C4.1 Duration of treatment too short	0	0	0
Treatment duration	C4.2 Treatment duration too long	38	9	47 (4.6)
Total		38	9	47 (4.6)

N = Total number of drug-related problems identified (i.e. 1026 drug-related problems)

Table 4: The Frequency of drug-related problem with causes as primary domains (continued)

Domain	Subdomain	Actual DRP	Potential DRP	total (%)
Cause 5	C5.1 Patient gets/takes drug on wrong times	23	20	43 (4.2)
Drug use process	C5.2 Drug under used/administered	5	4	9 (0.9)
	C5.3 Drug overused/administered	14	17	31 (3.0)
	C5.4 Drug not taken/not administered at all	97	32	129 (12.6)
	C5.5 Wrong drug taken/administered	0	2	2 (0.2)
	C5.6 Drug abused (unregulated overuse)	0	0	0
	C5.7 Patient unable to use drug/form as directed	0	0	0
Total		139	75	214 (20.9)
Cause 6	C6.1 Prescribed drug not available	60	23	83 (8.1)
Logistics	C6.2 Prescribing error (information wrong or missing)	37	22	59 (5.8)
	C6.3 Dispensing error (wrong drug or dose)	2	4	6 (0.6)
Total		99	49	148 (14.4)
Cause 7	C7.1 Patient forgets to take drug	0	0	0
Patient	C7.2 Patient uses unnecessary drug	0	0	0
	C7.3 Patient takes food that interacts	12	5	17 (1.7)
	C7.4 Patient stored drug inappropriately	0	0	0
Total		12	5	17 (1.7)
Cause 8	C8.1 Other cause	51	56	107 (10.4)
Other	C8.2 No obvious cause	0	0	0
Total		51	56	107 (10.4)

N = Total number of drug-related problems identified (i.e. 1026 drug-related problems)

DISCUSSION

During this three-month study, the pharmacist reviewed 2404 medication orders prescribed for 105 patients and identified 1026 DRPs. The rate of DRPs in the present study was 42.7 DRPs per 100 medication orders and approximately ten DRPs for each patient. Potential DRPs accounted for the majority of the cases as opposed to the manifest/actual DRPs. A higher rate of DRPs (81 DRPs per 100 medication orders) was reported from a study conducted in a teaching hospital in India. In addition, that study revealed that there was an upward tendency of DRP incidence in accordance to increased number of medications [19]. When comparing the rate of DRPs experienced by each patient, other studies involving either inpatient or outpatient settings uncovered lower rate which ranged between 1.4-5.0 DRPs/patient [20-25].

With respect to the profile of DRPs, non-allergic adverse drug events and sub-optimal effect of treatment were found as the major primary domains for DRP problems. Additionally, an inappropriate combination of drugs with other drugs or food contributed to the predominant cause of DRPs. These findings were in line with the DRP profiles documented by Rani *et al.* [19]. However, different DRP patterns were revealed in other studies with dosing-related problems being responsible for the most frequent DRPs [26, 27]. In relation to drugs associated with DRPs, the result of our study were consistent with those of previous studies where drugs for cardiovascular diseases (anti-platelets, anti-hypertensives) and drugs for correcting electrolyte imbalance (i.e. phosphate binders) were most commonly implicated in DRP incidence [20, 23, 25].

The consequences of DRPs have ramifications in CKD patients already burdened by multimodal treatment. It has been well-defined that the consequences of the DRPs result in prolonged hospitalisation, readmissions to the hospital, increased cost and premature death [28, 29]. It is evident that reducing the occurrence of DRPs will lead to better outcomes for patients, and reduce the financial burden [30]. In addition, there may also be great personal costs to those involved and may result in time away from work, low patient satisfaction and decreased public trust toward health care [31, 32]. Hence, it is of importance to implement effective measures to prevent and resolve DRP occurrence. As the part of health care professionals, pharmacists are best positioned to ensure that medications are used rationally and safely, increase awareness of DRPs, prevent and resolve the problems. The traditional role of pharmacists particularly in hospitals (e. g. compounding, dispensing and supply of medicines) has expanded to include clinical activities. This transition has increased the contribution of pharmacists as part of healthcare teams in minimising DRPs and optimising patient outcomes [33]. Understandably, the role of clinical pharmacists has been well-defined to improve patient safety and minimise any harm related to medication use in numerous clinical settings. Substantial savings can be made by maximising the competencies of pharmacists and implementing pharmaceutical care [34-37]. The results of the present study specifically support the established evidence that clinical pharmacists through identification, prevention and resolution of DRPs are able to provide quality patient care and ultimately improve desired clinical outcomes in patients with CKD [25, 38, 39].

The nature of prospective observation in this study offers more opportunities to capture DRPs in comparison to the retrospective method. In addition, the real-time measures through prevention of potential DRPs and resolution of actual DRPs benefit the patients during the study; not merely providing the data of rate and nature of DRPs. However, a number of limitations need to be acknowledged. This study was conducted in one hospital which diminishes the generalizability of the findings. Another limitation is the difficulty in drawing accurate comparisons with other DRP studies due to considerable variations in settings, design, duration, size and method.

CONCLUSION

This study uncovered higher rate of DRPs experienced by each patient compared to other CKD studies. In terms of types of DRPs, this study showed varied results as opposed to other CKD studies. The nature of prospective observation offers more opportunities to capture DRPs and to intercept potential DRPs. This study also justified the evident that pharmacists' competencies to identify DRPs, prevent potential DRPs and resolve actual DRPs are vital measures to improve clinical outcomes in CKD patients.

CONFLICT OF INTERESTS

The authors have none to declare

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