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Adverse drug events in hospitalized patients with chronic kidney disease

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Abstract. Background and objective: Adverse drug events (ADEs) are a common cause of hospitalization and in-hospital complications. The aim of this study was to determine the rates, types, severity and preventability of pre-admission and in-hospital ADEs in patients with chronic kidney disease (CKD). Methods: This study was conducted at the nephrology unit at Penang General Hospital. A random sample of 300 adult patients with CKD was included. Medical records and charts were reviewed by a clinical pharmacist every work day to find any evidence of errors or complications related to drug use. If a suspected ADE was found, further investigations were carried out to assess the causality, severity and preventability of the event. Results: A total of 159 ADEs were reported in 122 (40.7%) of the patients. We found 86 suspected pre-admission ADEs in 68 (22.7%) of the patients. These were either the cause of admission for some patients or discovered by the initial physical examination and laboratory investigations. During hospitalization, 64 (21.3%) patients had 73 suspected ADEs. Out of the total 159 suspected ADEs, it was highly probable that 31 events were due to medication, while 61 were of lower probability, and 67 were merely possible. A total of 48 (30.2%) events was considered preventable. 46 events (28.9%) were serious, 93 (58.5%) were less serious and 20 (12.6%) were insignificant. The medication classes most frequently involved in ADEs were diuretics, antibacterials, drugs used for diabetes mellitus, antithrombotic agents, mineral supplements and antihypertensive drugs. Conclusion: ADEs are very common in hospitalized CKD patients, and some of these events are preventable. The service of a clinical pharmacist may help to reduce ADEs.

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Introduction

Adverse drug events (ADEs) are a common cause of hospitalization and in-hospital complications, and are a considerable source of morbidity and mortality. The occurrence of ADEs significantly prolongs the length of hospital stay and increases costs [1, 2, 3]. Although there is an enormous amount of data regarding the incidences of ADEs, the precise frequency is unknown. Previous studies, however, have estimated that approximately 2.0 – 6.5% of all hospital admissions are due to ADEs [3, 4, 5] and that 2.0 – 20.0% of patients suffer from ADEs while staying in hospital [4, 6, 7, 8, 9]. Rates in outpatients have a range from 5 to 35% [10]. Many of these events cannot be avoided, but some are due to errors in management and are preventable. In a review the median preventability rate of ADEs in hospitals has been found to be 35.2% (range 18.7 – 73.2%) [11]. Epidemiological data support the existence of specific factors that increase the risk of adverse drug reactions (ADRs) and ADEs in general, such as female gender, age, serious illness, renal insufficiency, liver disease, polypharmacy and alcoholism [5, 12, 13]. The goal of studying the incidence, type, and preventability of ADEs and medication errors is to reduce the likelihood of harm related to medications and to improve the quality of health care delivery. For this, it is essential to describe the epidemiology of such problems accurately [14].

Patients with chronic kidney disease (CKD) often have alterations in pharmacokinetic parameters such as drug absorption, distribution, protein binding, metabolism and renal excretion. Many medications and their metabolites are eliminated by the kidney and thus adequate renal function is important to avoid toxicity. Patients with severe renal insufficiency can experience an accumulation of metabolites which can contribute to pharmacological activity or toxicity. Patients can also have an altered pharmacodynamic re-

sponse to a given drug due to physiological and biochemical changes associated with progressive renal insufficiency [13, 15, 16].

Drug-related problems are common in patients with renal insufficiency and those on hemodialysis. Factors associated with medication-related problems in these patients include: more than 3 present concurrent disease states; medication regimen changed 4 or more times during the past 12 months; 5 or more medications in present drug regimen; 12 or more medication doses per day; presence of drugs that require therapeutic monitoring and presence of diabetes. Nearly all CKD patients are at risk due to their present multiple risk factors [17]. Furthermore, they are usually noncompliant with medications [18, 19]. It has been shown that the incidence of drug-related problems and ADEs is much higher in patients with CKD than in those without renal insufficiency [20, 21]. Although numerous studies have evaluated the ADEs, information related to hospitalized patients with CKD is limited. The aim of this study was to determine the rate, type, severity and preventability of ADEs among hospitalized patients with CKD.

Methods

This prospective cohort study was conducted at the nephrology unit at Penang General Hospital, Malaysia. The study protocol was reviewed and approved by the Penang Hospital Research Ethics Committee. A standardized form specially designed for the conduct of the study was used for data collection. Data was obtained between January 1 and May 31, 2007. A random sample of 300 patients was chosen, which was approximately 50% of the admitted patients who met the inclusion criteria. To avoid bias, a random number generator was used to select patients randomly according to their admission numbers. Patients with CKD, an estimated creatinine clearance $\leq$ 50 ml/min at admission, $>$ 18 years and admitted to the nephrology unit for $>$ 24 h were included. Data was collected from the patients' medical records and charts, and included age, gender, race, weight, medical history and comorbidities, diagnostic tests, dialysis information, and drug therapy and dosage during hospitalization. The patients' medical records were reviewed every work day by a clinical pharmacist (PhD candidate) in order to detect evidence of errors or complications related to drug use. To detect ADEs and medication errors we used the method described by Morimoto et al. [14], defining ADE as "an injury resulting from the use of a drug" [22]. Under this definition, the term ADE includes adverse drug reactions (ADRs) and harm resulting from medication errors. We used the World Health Organization (WHO) definition of ADR, defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiologic function" [23]. A medication error was defined as "an inappropriate use of a drug that may or may not result in harm" [22]. For medication errors, we included only those that caused harm. If a suspected ADE was discovered, further investigation was carried out to assess the causal relationship between the suspected drug and event using the Naranjo algorithm [24].

Events were classified as preventable and non-preventable. Preventable ADEs were those that could have been avoided by appropriate drug selection or management. We determined preventability on the basis of physician's presumed knowledge at the time of drug prescribing. We assumed the physician's decision was correct and the ADE was non-preventable if insufficient information that could affect the treatment choice was available at the time of prescribing the medications. If an event was preventable, we specified the type of error [10].

To evaluate the seriousness of ADEs, we used the definition of serious ADEs of the Food and Drug Administration (FDA), which includes events that "result in death, a life-threatening condition, initial or extended hospitalization, persistent or significant disability, cancer, and congenital abnormalities". Adverse drug events that did not meet this definition but still required treatment were defined as significant. Finally, events that did not require treatment were defined as mild or insignificant [22].

We looked for ADEs occurring while staying in hospital as well as ADEs that occurred prior to admission. For laboratory medical tests, any value below or above nor-

Table 1. Demographic and clinical characteristics of patients.

Characteristics	Patients without ADEs	Patients with ADEs	p value
Gender, n (%)			0.306
Male	104 (58.4)	64 (52.5)	
Female	74 (41.6)	58 (47.5)	
Ethnic group, n (%)			0.313
Chinese	85 (47.8)	68 (55.7)	
Malay	63 (35.4)	34 (27.9)	
Indian	28 (15.7)	20 (16.4)	
Others	2 (1.1)	0 (0.0)	
Stage of chronic kidney disease, n (%)			0.068
Stage 5 (ESRD)	164 (92.1)	102 (83.6)	
Stage 4	9 (5.1)	14 (11.5)	
Stage 3	5 (2.8)	6 (4.9)	
Age, mean ± SD	55.83 ± 13.1	55.17 ± 15.6	0.703
Number of comorbidities, mean ± SD	3.08 ± 1.3	3.45 ± 1.27	**0.015**
Number of drugs used, mean ± SD	8.55 ± 3.2	10.60 ± 3.9	**0.0001**
Duration of hospital stay, mean ± SD	4.97 ± 5.6	8.23 ± 9.3	**0.001**

mal range used by the hospital medical laboratories was considered abnormal.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) software program (version 15). Data is presented as mean ± SD or count and percentage when appropriate. For 2-sample comparison of continuous variables, the t-test was used. Categorical comparisons were made using χ^2-test. Spearman's correlation was performed to determine whether associations existed between ADEs and age, number of medications, number of comorbidities, and length of hospital stay. p values < 0.05 were considered significant.

Results

A total of 300 patients were randomly selected, most of them were end-stage renal disease patients (ESRD). Of the 300 patients, 122 (40.7%) had a suspected ADE with a total of 159 events. In 68 (22.7%) patients, we found 86 suspected pre-admission ADEs, which were either the cause of admission or were discovered by initial physical examination and laboratory investigations. During hospitalization, 73 suspected ADEs were found in 64 (21.3%) patients. A comparison between characteristics of patients without ADEs and those who had events (either pre-admission or during hospitalization) are shown in Table 1. Adverse drug events positively correlated with the number of medications used during hospitalization (Spearman's rank correlation coefficient (rs) = 0.287, $p < 0.0001$), number of comorbidities ($rs = 0.113$, $p < 0.05$) and the duration of hospital stay ($rs = 0.298$, $p < 0.0001$). The mean number of comorbidities, mean number of medications, and the duration of hospital stay were significantly higher for patients who had ADEs compared to those who did not have any ADEs. The mean number of comorbid conditions was 3.45 ± 1.27 in patients with ADEs while it was 3.08 ± 1.3 in the other group ($p < 0.05$). The mean number of medications during hospitalization was 10.60 ± 3.9 in patients with ADEs versus 8.55 ± 3.2 in patients without them ($p < 0.001$). The mean duration of hospitalization of patients with ADEs was 8.23 ± 9.3 compared to 4.97 ± 5.6 in patients without ADEs ($p < 0.001$). There were no significant differences in gender, ethnic group, age and stage of chronic kidney disease between the two groups.

To assess the causal relationship between the suspected drug and event we used the Naranjo algorithm and found that 31 events

Table 2. Reasons for preventable ADEs.

Reason	Frequency	Percentage (%)
Dose or frequency was not appropriate	20	41.7
Drugs involved were not appropriate for the patient's clinical condition	15	31.3
Required therapeutic drug monitoring or other necessary laboratory tests were not performed	7	14.6
A known drug interaction was the suspected cause of the reaction	4	8.3
Others	2	4.2
Total	48	100

Table 3. Drug class most commonly associated with ADEs.

Drug class	Frequency	Percentage (%)
Diuretics	34	21.4
Antibacterials	26	16.4
Drugs used in diabetes	25	15.7
Antithrombotic agents	12	7.5
Mineral supplements	12	7.5
Serum lipid reducing agents	11	6.9
Agents acting on renin-angiotensin system	9	5.7
Beta blocking agents	8	5.0
Calcium channel blockers	6	3.8
Corticosteroids	5	3.1
Others	11	6.9
Total	159	100

Table 4. Body system most commonly associated with ADEs.

System affected	Frequency	Percentage (%)
Metabolic	45	28.3
Endocrine	29	18.2
Cardiovascular	25	15.7
Gastrointestinal	24	15.1
Hematological	10	6.3
Neuromuscular	6	3.8
Hepatic	5	3.1
Central nervous	2	1.3
Dermatologic	2	1.3
Renal	1	0.6
Respiratory	1	0.6
Others	9	5.7
Total	159	100

were highly probable, 61 were probable and 67 were only possibly due to the medication.

When we evaluated the preventability of events, 48 (30.2%) of the events were possibly preventable while 111 (69.8%) were unpreventable. The causes of preventable events are shown in Table 2.

Regarding the seriousness of events, 46 (28.9%) were serious, 93 (58.5%) were significant and 20 (12.6%) were insignificant. Serious ADEs included symptomatic electrolyte disturbances, severe hypotension, severe hypoglycemia, neutropenia, intestinal bleeding and respiratory depression. Examples of significant ADEs included mild hypoglycemia, mild electrolyte disturbances, mild hypotension, myalgia, diarrhea, vomiting and epigastric pain that required therapeutic interventions. Insignificant events included hypoglycemia, electrolyte disturbances, diarrhea, nausea and vomiting that were abnormal or bothersome but did not require any treatment.

The medication classes most frequently involved in ADEs were diuretics, antibacterials, drugs used for diabetes mellitus, antithrombotic agents, mineral supplements and antihypertensive drugs (Table 3). The systems most commonly affected by ADEs were the metabolic, endocrine, cardiovascular, gastrointestinal and hematological systems (Table 4).

Discussion

The precise frequency of ADEs is unknown. It has been estimated that approximately 2.0 – 6.5% of all hospital admissions are related to ADEs [3, 4, 5] and that 2.0 – 20.0% of patients suffer from ADEs while in hospital [4, 6, 7, 8, 9]. There are many different methods for definition, causality assessment, severity classification and detection, making it difficult to compare different studies [25]. In 1998, a meta-analysis of studies conducted in the United States over 32 years found that the overall incidence of ADRs, including patients admitted to hospital due to an ADR and those experiencing one in hospital, was 15.1% of hospitalized patients, and 6.7% of those were serious [8]. In our study, 86 pre-admission ADEs were found in 22.7% of patients, and 73 suspected ADEs were found in 21.3% of patients during hospitalization. Compared to other studies, both incidences

are considered high, which suggests that renal impairment is a risk factor for ADEs.

The problems brought about by ADEs are important and costly to hospitals. Because a notable number of ADEs is considered avoidable, it seems logical to focus on their prevention. Increasing the knowledge and understanding of ADEs may help to prevent a higher proportion of ADEs [25]. Most ADEs in our study were unfortunately unavoidable, but 30.2% of them were avoidable, showing there is room for improvement. Most of the preventable ADEs in our study were due to inappropriate dose or frequency, drugs inappropriate for the patient's clinical condition, inadequate laboratory test monitoring and/or known drug interactions. In a literature review regarding the nature of preventable ADEs in hospitals, the median preventability rate was 35.2 (range 18.7 – 73.2%) and dosing errors were the most often associated cause (22.4%). The second most common cause was inappropriate drug choice (17.0%) [11]. A study of ADEs in hospitalized cardiac patients found that the most common errors were incorrect frequency or rate of medication administration (29.7%) and wrong dosage (13.0%) [6]. Our results are similar to other studies, suggesting that some ADEs are due to inadequate monitoring of therapies and doses.

Leape et al. [26] found that the most common cause of ADEs was the dissemination of drug knowledge, particularly to physicians, who made multiple prescription errors that appeared to be due to deficiencies in drug knowledge. These included incorrect doses, dosage forms, dosage regimen and routes of administration, as well as errors in the choice of drugs. Inadequate availability of patient information was another major cause of error [26]. The principal cause of problems, however, is insufficient information when the prescribing decisions are made. Two interesting strategies of prevention, pharmacist participation on ward rounds and computerized physician order entry with a clinical decision support system, have been shown to be useful [25]. In our hospital, physician orders in wards are paper-based, however the opinion of a clinical pharmacist could be helpful. Having a pharmacist in a team in the intensive care unit (ICU) and general medical units has been shown to reduce preventable ADEs [27, 28]. Furthermore, pharmacists providing pharmaceutical care services has been shown to improve medication compliance, provide drug information, raise awareness of inappropriate medication prescription and improve therapeutic response to medications [7, 20, 21], as well as to improve ESRD patient care [29]. Therefore careful and continual monitoring of patient profiles by clinical pharmacists could lead to a decrease in ADEs.

The drug classes associated with ADEs are not surprising because they are the most common classes used in patients. Understanding ADEs would be helpful in prescribing these medications appropriately. The body systems affected are also predictable, as CKD patients are typically subject to electrolyte disturbances, hypoglycemia, gastrointestinal and hematological complications.

One limitation of our study is that we considered any laboratory value outside the normal range as abnormal, which may have led to an overestimation of ADEs. In conclusion, however, we can say that our study supports the notion that ADEs are common in CKD patients and provides a "real-life" picture of ADEs that affect CKD patients. Furthermore, our study may be helpful in efforts to improve patient safety.

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