ปัญหาจากการใช้ยาในการจัดการความผิดปกติของสมดุลแร่ธาตุและกระดูกในผู้ป่วยไตวายระยะสุดท้ายที่รอรับการปลูกถ่ายไต ณ โรงพยาบาลจุฬาลงกรณ์

Drug-Related Problems in the Management of Disturbance of Mineral and Bone Metabolism in ESRD Patients Awaiting Renal Transplantation at King Chulalongkorn Memorial Hospital

นิพนธ์ต้นฉบับ

Original Article

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วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2556;8(2):58-65

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความชุกและลักษณะของปัญหาจากการใช้ยา รวมถึงยาที่เป็นสาเหตุของปัญหา ในการควบคุมความผิดปกติของสมดุลแร่ธาตุและกระดูกในผู้ป่วยไตวายระยะสุดท้ายที่รอรับการปลูกถ่ายไต **วิธีการศึกษา:** การวิจัยนี้เป็นการศึกษาเชิงพรรณนา ทำการศึกษาที่คลินิกผู้ป่วยก่อนการปลูกถ่ายไต (Pre-KT Clinic) โรงพยาบาลจุฬาลงกรณ์ เก็บข้อมูลที่จุดเวลาหนึ่ง (cross-sectional study) ในผู้ป่วยที่อยู่ในรายชื่อรอรับการปลูกถ่ายไตที่โรงพยาบาลจุฬาลงกรณ์ทุกคน ซึ่งมีนัดตรวจประเมินความพร้อมของร่างกายก่อนการปลูกถ่ายไตตั้งแต่เดือนกรกฎาคม 2554 ถึงกุมภาพันธ์ 2555 เภสัชกรคลินิกเป็นผู้ประเมินว่าผู้ป่วยมีปัญหาจากการใช้ยาหรือไม่ ปัญหาจากการใช้ยาที่พบถูกจัดแบ่งประเภทโดยใช้เกณฑ์ของ Cipolle และคณะ และยืนยันความถูกต้องโดยเภสัชกรผู้เชี่ยวชาญภายนอก **ผลการศึกษา:** จากผู้ป่วยทั้งหมด 112 คน พบว่า 71 คน (ร้อยละ 63.39) มีปัญหาจากการใช้ยาในการควบคุมความผิดปกติเกี่ยวกับแมแทบอลิซึมของแคลเซียม ฟอสฟอรัส และฮอร์โมนพาราไทรอยด์ พบปัญหาจากการใช้ยา 97 ปัญหา คิดเป็น 0.87 ปัญหาต่อผู้ป่วย ปัญหาที่พบมากที่สุดคือ ปัญหาความร่วมมือในการใช้ยา (ร้อยละ 30.93) รองลงมาคือ ปัญหาความปลอดภัยในการใช้ยา (ร้อยละ 25.78) รายการยาที่เกี่ยวข้องมากที่สุดคือ calcium salts (ร้อยละ 43.30) รองลงมาคือ vitamin D sterols (ร้อยละ 31.96) **สรุป:** ประมาณ 2 ใน 3 ของผู้ป่วยที่รอรับการปลูกถ่ายไตมีปัญหาจากการใช้ยาในการควบคุมความผิดปกติของสมดุลแร่ธาตุและกระดูก ความไม่ร่วมมือในการใช้ยาเป็นปัญหาที่พบมากที่สุด และ calcium salts เป็นรายการยาที่พบปัญหามากที่สุด

คำสำคัญ: ปัญหาจากการใช้ยา, ผู้ป่วยที่รอรับการปลูกถ่ายไต, แมแทบอลิซึมของกระดูกและแร่ธาตุ, ภาวะไตวายระยะสุดท้าย

Abstract

Objective: To determine the prevalence, category, medications related to drug-related problems in the management of abnormalities in calcium, phosphate, and bone metabolism in ESRD patients on the waiting list for renal transplantation. **Method:** A cross-sectional descriptive study was conducted in kidney transplant candidates listed at the Pre-KT clinic, King Chulalongkorn Memorial Hospital. All patients who had their appointment for regular pre-transplantation evaluation from July 2011 to February 2012 were enrolled in this study. Drug-related problems were identified by a clinical pharmacist using the criteria described by Cipolle and were confirmed by external expert opinion. **Results:** Of the 112 patients, 71 (63.39%) had DRPs related to calcium, phosphorus, and parathyroid hormone metabolism disorders. A total of 97 DRPs were detected, representing 0.87 DRPs per patient. The most common DRP identified were noncompliance to drug therapy (30.93%) and safety-related problems (25.78%), respectively. The medicines most frequently involved were calcium salts (43.30%) and vitamin D sterols (31.96%). **Conclusion:** DRPs in the management of renal bone disease occurred in about two-thirds of ESRD patients awaiting renal transplantation. Patients' noncompliance to drug therapy was the most common type of DRPs found. Calcium salts were the most frequent medicine involved in our setting.

Keywords: drug-related problems, kidney transplant candidates, bone and mineral metabolism, end-stage renal disease

Introduction

Abnormalities in calcium, phosphate, and bone metabolism commonly occur in end-stage renal disease (ESRD) and kidney transplant patients.[1-3] Numerous studies showed that these derangements are associated with increased mortality in patients with chronic kidney disease (CKD).[1,2,4] A large study of patients on chronic dialysis found that a serum phosphorus level above 6.0 mg/dl was associated with increased risk for all-cause and cardiovascular mortality.[4] An elevated Ca x PO_4 product greater than 55 mg^2/dl was also associated with increased mortality risk.[5] Hyperphosphatemia is an important factor in the development of secondary hyperparathyroidism (SHPT) that is associated with an increased risk of cardiovascular death.[6] Early management in the calcium and phosphorus metabolism is a critical aspect of successful treatment and provides further benefits in controlling SHPT. Patient compliance with prescribed therapy plays a vital role in achieving treatment goals.[7]

Drug-related problems (DRPs) are common in dialysis patients.[8] These patients have a high intake of medications. They typically take > 10 different types of medications to treat, on average, 5 to 6 medical conditions, and are more likely to develop DRPs.[9] In addition, they patients have been reported to be noncompliant with several medications commonly prescribed in this population.[10-14] To date, the prevalence of DRPs in the management of disturbances of mineral and bone metabolism is still unknown in patients awaiting renal transplantation at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand. These patients differ from the population of CKD patients, because they had already been selected to exclude the most severely ill patients. Besides, they have a hope of living long and well after transplantation. Cardiovascular events are the major causes of death in patients following renal transplantation.[15] Good control of cardiovascular risk factors is important for transplant candidates since disturbances of mineral and bone metabolism are associated with cardiovascular mortality. In this study, we conducted a cross-sectional study to assess the prevalence, category, medications involved of drug-related problems in the management of abnormalities in calcium, phosphate, and bone metabolism in ESRD patients already placed on the waiting list of renal transplantation at KCMH.

Methods

Setting and participants

The participants of the current study were kidney transplant candidates registered on the waiting list of KCMH. All patients who had their appointment for regular pre-transplantation evaluation (every 3 - 6 months after listing) from 27th July 2011 to 22nd February 2012 at the pre-KT clinic were enrolled in this study. We excluded patients who (1) did not return for follow-up during this period, (2) had already received a renal transplant before a study visit, and (3) refused to sign informed consents.

In this study, CKD-MBD related DRPs were drug-related problems associated with the management of chronic kidney disease-mineral and bone disorder. A patient was identified as having CKD-MBD related DRPs only when either the serum phosphorus level (PO_4), the serum corrected total calcium level (Ca), the serum calcium-phosphorus product (Ca x PO_4), or the serum intact parathyroid hormone level (iPTH) was outside the target range recommended by the 2003 KDOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease (PO_4; 3.5-5.5 mg/dL, Ca; 8.4-9.5 mg/dL, Ca x PO_4; < 55 mg^2/dL^2, iPTH; 150-300 pg/ml) which involved drug therapy.

Data collection

This study consisted of 2 periods: a screening period and a study period. During the screening period, we collected retrospective data of the prior 3 visits to screen patients who were prone to have CKD-MBD related DRPs before entering the study period. During the screening period, a clinical pharmacist reviewed the patient profile of the previous 3 visits and evaluated whether the laboratory measurement (the serum levels of corrected total calcium, phosphorus, and intact plasma parathyroid hormone) was within the target range recommended by the 2003 KDOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease. In order to assure the accuracy of identified DRPs, we included only patients who had an extending problem over a period of time not those who had temporary fluctuations of some markers. Patients were evaluated appropriate for medical therapy in the study visit when the prior 2 out of 3 measurements or the most recent previous value were outside the range. The study period took place on the day patients came to pre-KT clinic for pre-transplantation evaluation (normally every 3 - 6 months). All patients in the study visit were counseled by one clinical pharmacist to ensure their compliance to pharmaco-therapeutic regimen and were assessed individually for identifying CKD-MBD related DRP using the criteria described by Cipolle.[16] All patients received standard dietary and drug counseling in the study visit. Any dietary and drug-related problem found was resolved promptly in the study visit by the clinical pharmacist.

Data including patient characteristics, past medication lists, comorbid health problems, all related laboratory data, and physical exam results were obtained from the patients' pre-transplantation re-evaluation medical records. Data including current medication lists, medicine allergies history and DRPs were collected by pharmacist interviewing patients and/or their relatives in the study visit.

Outcome measures

The primary outcome was the prevalence of CKD-MBD related DRPs in ESRD patients on the waiting list for renal transplantation. The secondary outcomes were the prevalence of CKD-MBD related DRPs in each category and medications associated. The CKD-MBD related DRPs in this study were classified into 7 different categories according to Cipolle's classification[16]: unnecessary drug therapy (UND), need for additional drug therapy (NAD), ineffective drug (IED), dosage too low (DTL), adverse drug reaction (ADR), dosage too high (DTH), and noncompliance to drug therapy (NCP). In addition, UND and NAD were grouped and categorized as indication-related drug related needs. IED and DTL were grouped and categorized as effectiveness-related drug-related needs. ADR and DTH were grouped and categorized as safety-related drug-related needs. NCP were categorized as compliance-related drug-related needs. Categorizations were confirmed by an external expert pharmacist. Disagreements were discussed and resolved by consensus.

Statistical analysis

Data were analyzed and expressed as geometric mean $\pm$ SD, when appropriate. Frequency data were presented as percentage or count. The percentage of patients with CKD-MBD related DRPs was determined as follows: {(number of patients with CKD-MBD related DRPs) x 100} /number of patients enrolled in this study. An average number of CKD-MBD related DRPs per patient was calculated as follows: the total number of CKD-MBD related DRPs identified /number of patients enrolled in this study. All calculations were performed using Microsoft Excel 2007 and SPSS for Windows version 17.0 (SPSS. Co., Ltd., Bangkok Thailand).

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University (IRB No. 160/54). Informed consent was received from all patients.

Results

One hundred and twelve patients were enrolled into this study. Eighty-three patients who had the prior 2 out of 3 laboratory measurements or the most recent previous value outside the range entered the study period and were assessed for CKD-MBD related DRPs in the study visit. CKD-MBD related DRPs were found in 71 patients. Categories and common causes of drug-related problems in this study are shown in Table 1. All patients came from several hospitals to be registered on the KCMH transplant waiting list and we were not the main healthcare providers for their chronic care.

Table 2 summarizes their demographics. Overall, patients were an average of 45.4 $\pm$ 11.8 years old and were taking 11.05 $\pm$ 3.25 items of medications at one time point. 55.4% of patients were male and 98.2 % of patients received hemodialysis. The weight status was normal (BMI 22.5 $\pm$ 3.9) and the mean waiting time for kidneys was 3.34 $\pm$ 1.87 years.

Patient medications used in the management of renal bone disease in our study are illustrated in Table 3. There were 3 kinds of phosphate binders used in our patients: calcium salts (61.8%), Aluminium salts (25.5%), and lanthanum carbonate (12.7%). And there were 2 vitamin D sterols seen in the study: alfacalcidol and calcitriol. Alfacalcidol was found the most frequently prescribed (68.3%).

A mean serum level of corrected total calcium and intact parathyroid hormone were not accomplishing the treatment goal (9.56 $\pm$ 0.97 mg/dL and 450.30 $\pm$ 452.83, respectively), whereas an average serum phosphorus level and Ca x PO_4 product were within the target range (5.4 $\pm$ 1.77 mg/dL and 51.48 $\pm$ 17.21 mg^2/dL^2) (Table 4).

Table 5 presents the distribution of laboratory values in different ranges. The proportion of patients whose serum corrected total calcium, serum phosphate, Ca x PO_4 product, and intact parathyroid hormone levels were within the target range accounted for 38%, 49%, 60.6% and 24%, respectively. Concerning serious levels associated with increasing mortality risk[4], 28.7% of patients had corrected total calcium levels greater than 10.0 mg/dL. 1% and 33.7% of patients had phosphate levels of 2 mg/dL or less and above 6.0 mg/dL, respectively. Ca x PO_4 product levels were of 55 mg^2/dL^2 or more in 39.4% of patients. Intact parathyroid hormone levels greater than 600 pg/mL were found in 24% of patients.

Table 1 Categories and common causes of drug-related problems in this study.

DRPs*	Common causes of drug-related problems*	Examples**
1. Unnecessary drug therapy	1.1 There is no valid medical indication for the drug therapy at this time. 1.2 Multiple drug products are being used for a condition that requires single drug therapy. 1.3 The medical condition is more appropriately treated with non-drug therapy. 1.4 Drug therapy is being taken to treat an avoidable adverse reaction associated with another medication. 1.5 Drug abuse, alcohol use, or smoking is causing the problem.	*A patient did not stop taking vitamin D sterols despite her serum level of iPTH as low as 30 pg/mL.*
2. Need for additional drug therapy	2.1 A medical condition requires the initiation of drug therapy. 2.2 A medical condition requires additional pharmacotherapy to attain synergistic or additive effects. 2.3 Preventive drug therapy is required to reduce the risk of developing a new condition.	*A patient with SHPT has not received vitamin D therapy for controlling his elevated iPTH level (iPTH 880.2 pg/mL).* *(In this study, even in cases where phosphorus levels were also high, DRPs were still assigned into this category and were counted twice as phosphorus and iPTH problems. In cases where only phosphorus levels were high while iPTH level were normal or unknown, DRPs were counted once as phosphorus problems)*
3. Ineffective drug	3.1 The drug is not the most effective for the medical problem. 3.2 The medical condition is refractory to the drug product. 3.3 The dosage form of the drug product is inappropriate. 3.4 The drug product is not an effective product for the indication being treated.	*A patient with serum phosphorus level as high as 7.3 mg/dL had been taking 5,000 mg per day of calcium carbonate for 12 months.*
4. Dosage too low	4.1 The dose is too low to produce the desired response. 4.2 A drug interaction reduces the amount of active drug available. 4.3 The dosage interval is too infrequent to produce the desired response. 4.4 The duration of drug therapy is too short to produce the desired response.	*A patient's 1.0 mcg thrice daily dose of alfacalcidol was not enough to control her iPTH level (her iPTH level increased from 527.1 pg/mL to 986 pg/mL in the last 9 months while her serum calcium and phosphorus level were still within the normal range)*
5. Adverse drug reaction	5.1 A safer drug product is required due to risk factors. 5.2 The drug product causes an undesirable reaction that is not dose-related. 5.3 A drug interaction causes an undesirable reaction that is not dose-related. 5.4 The dosage regimen was administered or changed too rapidly. 5.5 The drug product causes an allergic reaction. 5.6 The drug product is contraindicated due to risk factors.	*A patient developed hypercalcemia (serum calcium level as high as 11.6 mg/dL) associated with calcium carbonate used for controlling his hyperphosphatemia.*
6. Dosage too high	6.1 Dose is too high. 6.2 The dosing frequency is too short. 6.3 The duration of drug therapy is too long. 6.4 A drug interaction occurs resulting in a toxic reaction to the drug product. 6.5 The dose of the drug was administered too rapidly.	*A patient with her iPTH level as low as 70.6 pg/mL with serum corrected total calcium level of 9.18 mg/dL and no history of parathyriodectomy should have their dose of calcium carbonate decreased in order to keep serum phosphorus level at upper target/ normal range to stimulate the production of PTH.*
7. Noncompliance to drug therapy	7.1 The patient does not understand the instructions. 7.2 The patient forgets to take the medications. 7.3 The patient prefers not to take the medication. 7.4 The drug product is too expensive for the patient. 7.5 The patient cannot swallow or self-administer the drug product appropriately. 7.6 The drug product is not available for the patient.	*A patient did not chew his aluminium hydroxide tablets before swallowing because he did not understand the correct usage of phosphate binders.*

* Categories and common causes of DRPs were defined by Cipole et al.[16] The common causes are arranged in order of frequency from the most to the least found in this study.

** Examples show the real cases of the most frequently cause of DRPs found in each category.

Table 2 Summary of patient demographics.

Patient Characteristic	N = 112
Age (years)	45.4 ± 11.8
Male gender (%)	55.4
BMI (kg/m^2)	22.5 ± 3.9
Smoking (%)	5.4
Past history of CVD (%)	19.6
Family history of CVD (%)	11.6
Hemodialysis (%)	98.2
Peritoneal dialysis (%)	1.8
Duration of dialysis (years)	4.65 ± 2.37
Waiting time (years)	3.34 ± 1.87
No. of medication (items)	11.05 ± 3.25

Table 3 Distribution of types of patient medication used in the management of renal bone disease in the study visit.

Medications	No. of patients (%)
Phosphate binders	
Calcium salts	68 (61.8)
Aluminium salts	28 (25.5)
Lanthannum carbonate	14 (12.7)
Vitamin D sterols	
Alfacalcidol	28 (68.3)
Calcitriol	13 (31.7)

Table 4 Laboratory values in the study visit.

Laboratory values	Mean ± SD (n=112)	Range		Median
		Min	Max	
Serum calcium (mg/dL)	9.49 ± 1.01	6.70	12.40	9.50
Serum corrected total calcium (mg/dL)	9.56 ± 0.97	6.78	12.48	9.59
Serum phosphorus (mg/dL)	5.4 ± 1.77	2.0	11.2	5.1
Ca x PO_4 product (mg^2/dL^2)	51.48 ± 17.21	13.56	99.46	47.87
Intact parathyroid hormone (pg/mL)	450.3 ± 452.83	30.0	2109.0	267.0

Table 5 Distribution of laboratory values during the study visit.

Laboratory values	No. of patients (%)
Serum corrected total calcium level (mg/dL)	
Ca < 8.4	12 (11.1)
Ca 8.4 - 9.5*	41 (38.0)
Ca 9.6 - 10.0	24 (22.2)
Ca > 10.0	31 (28.7)
Serum phosphorus level (mg/dL)	
$PO_4 \leq 2$	1 (1.0)
PO_4 2.1 - 3.4	10 (9.6)
PO_4 3.5 - 5.5*	51 (49.0)
PO_4 5.6 - 6.0	7 (6.7)
PO_4 > 6.0	35 (33.7)
Ca x PO_4 product (mg^2/dL^2)	
Ca x PO_4 < 55*	63 (60.6)
Ca x $PO_4 \geq 55$	41 (39.4)
Intact parathyroid hormone (pg/mL)	
PTH < 150	15 (30)
PTH 150 - 300 *	12 (24)
PTH 301 - 600	11 (22)
PTH > 600	12 (24)

* Target range recommended by the 2003 KDOQI Clinical Practice Guideline for Bone Metabolism and Disease in Chronic Kidney Disease.

Of the 112 patients, 71 (63.39%) had CKD-MBD related DRPs. A total of 97 CKD-MBD related DRPs were detected, representing 0.87 CKD-MBD related DRPs per patient. As shown in Figure 1, the most common CKD-MBD related DRPs identified were noncompliance to drug therapy (30.93%) and safety-related problems (25.78%), respectively. Safety related problems were associated mainly with adverse drug reactions (18.56%). Ineffectiveness (18.55%) was related greatly to dosage too low (16.49%). Indication related problems (24.74%) were principally caused by need for additional drug therapy (19.59%). Of the 4 kinds of medicine related to CKD-MBD related DRPs in table 6, the most frequently involved was calcium salts (43.30%); vitamin D sterols were the second most. (31.96%). Noncompliance to drug therapy was the principle cause of calcium salts related DRPs (28.57%). Most of vitamin D sterols related DRPs were need for additional drug therapy (45.16%).

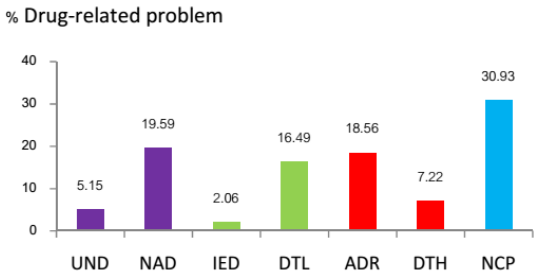

Figure 1 Frequency distribution of CKD-MBD related DRPs.

Abbreviation: UND = unnecessary drug therapy; NAD = need for additional drug therapy; IED = ineffective drug; DTL=dosage too low; ADR=adverse drug reactions; DTH=dosage too high; NCP=noncompliance to drug therapy.

Table 6: Frequency of each category of CKD-MBD related DRPs and medications associated.

Related drugs	Indication		Effectiveness		Safety		Compliance	Total DRPs
	UND	NAD	IED	DTL	ADR	DTH	NCP	
Vitamin D sterols	2 (6.45%)	14 (45.16%)	0 (0%)	6 (19.35%)	1 (3.23%)	0 (0%)	8 (25.81%)	31 (31.96%)
Phosphate binders								
Calcium salts	2 (4.76%)	4 (9.52%)	2 (4.76%)	5 (11.90%)	11 (26.19%)	6 (14.29%)	12(28.57%)	42 (43.30%)
Aluminium salts	1 (6.25%)	0 (0%)	0 (0%)	1 (6.25%)	6 (37.50%)	0 (0%)	8 (50.00%)	16 (16.49%)
Lanthanum	0 (0%)	1 (12.50%)	0 (0%)	4 (50.00%)	0 (0%)	1 (12.50%)	2 (25.00%)	8 (8.25%)
	5	19	2	16	18	7	30	97

Abbreviation: UND = unnecessary drug therapy; NAD = need for additional drug therapy; IED = ineffective drug; DTL = dosage too low; ADR = adverse drug reactions; DTH = dosage too high; NCP = noncompliance to drug therapy.

Discussions and Conclusions

The purpose of this study was to assess the prevalence of the CKD-MBD related DRPs. We found that 63.39% of the patients had CKD-MBD related DRPs and 0.87 CKD-MBD related DRPs per patient was identified. A previous pooled analysis of medication-related problems in ambulatory hemodialysis patients found 1,593 DRPs in 395 patients (4.03 DRPs per patients). Nephrology-specific medications (renal bone disease and anemia medications) accounted for 15.5% of identified DRPs.[8] Direct comparison with the previous studies is difficult because we assessed DRPs only in the management of renal bone disease. Nevertheless, the prevalence of CKD-MBD related DRPs in our study may be underestimated. The reason for this is that a number of patients who had laboratory measurements in the study visit outside the range whereas the prior at least 2 out of 3 measurements and the most recent previous value were inside the range were not assessed for CKD-MBD related DRPs by a clinical pharmacist due to our study criteria. These cases were not included to identify DRPs because they were more likely to be accidental fluctuations of the disease than actual problems.

Noncompliance to drug therapy was the most common type of CKD-MBD related DRPs (30.93%). In addition, calcium salts, the most commonly used phosphate binders, were the leading cause of CKD-MBD related DRPs (43.30%) and the most frequent calcium salts related DRPs (28.57%) were noncompliance to drug therapy. This finding is supported by previous studies, in those 13 studies in patients with end-stage renal disease reported the high percentage rate of noncompliance patients to phosphate binders ranged from 22-74%.[7] It is possible that the wide variation in the reported rates of noncompliance to drug therapy may be partially attributable to the differences in the methods and the definition used to measure them. The cutoff point used in those studies to identify noncompliance to drug therapy in phosphate level were ranged from 4.5 mg/dl to 7.5 mg/dl.[7] In our study, we used 5.5 mg/dl recommended by KDOQI guideline because this value is the objective of the nephrologist to adjust the regimen of phosphate binders. The reason why the KDIGO guideline was not used in this study is its more strictly recommendation that makes hard to implement in our setting since we were not the main healthcare providers, consequently, prevalence of DRPs reported in this study represents the minimum estimate. It is likely that phosphate binders were prone to cause noncompliance to drug therapy in the current study because of its complex regimens that may have no noticeable effect of noncompliance.

The two main strategies to control serum phosphate level are the use of phosphate binders and reduction of dietary phosphate intake. Patient compliance is an important issue in achieving an optimum phosphate level. About phosphate binders, timing is important when taking them. These can provide the maximum benefit when taken with meals and chewed completely before swallowing. In contrast, a lot of patients in this study took phosphate binders after meals or had several small meals during the day without taking phosphate binders at the same time. Some patients did not chew the medicine since they either disliked the taste or did not understand the correct usage of phosphate binders. Some forgot to take the medicine and some were not willing to take it. Furthermore, dietary phosphate restriction is also essential in controlling serum phosphate. Many patients in our study did not limit high-phosphate food intake due to lack of phosphate knowledge or poor perception of medical complications associated with hyperphosphatemia. Healthcare providers should inform this knowledge to their patients. For the reasons mentioned above, noncompliance to drug therapy found in this study were caused by patients themselves or healthcare professionals and these appeared to be preventable due to Schumock and Thornton's criteria.[17]

Safety related problems were the second most frequent CKD-MBD related DRPs found in the current study (25.78%). These were related mainly to adverse drug reactions (18.56%). Calcium salts were the medications most commonly implicated in this category of DRPs (61.11%). Calcium salts associated ADR were caused due to several reasons. Firstly, we found that a lot of patients required calcium salts to be discontinued because it was unsafe to the patients due to their risk factors, for example, failure to discontinue calcium salts in patients with risk of a dynamic bone disease (a high level of serum calcium with a low level of serum phosphate and intact parathyroid hormone). This problem could be solved by increasing attention from multidisciplinary dialysis staff team. Secondly, a number of patients needed to switch from calcium salts to other safer medicines; e.g. failure to change from calcium-based phosphate binders to noncalcium-based phosphate binders

in patients with hyperphosphatemia plus serum calcium > 10.2 mg/dl. It may be due to the unavailability of the safer medicines in their setting, the improper treatment monitoring from the dialysis staffs, or the unaffordable medication prices for patients. When these problems were assessed by Schumock and Thornton's criteria[17], most of ADR in this study were preventable.

Regarding vitamin D sterols related DRPs, these were related mainly to need for additional drug therapy (45.16%). Many individuals needed vitamin D sterols for the treatment of hyperparathyroidism but it was not prescribed. Most of these cases had serum calcium and/or serum phosphate levels above the target range so vitamin D sterols could not be started until serum calcium and serum phosphate levels were under control. This could be solved by using cinacalcet to decrease iPTH levels instead of vitamin D sterols, however, this medicine has not been registered in Thailand.

Effectiveness related problems were the least frequent CKD-MBD related DRPs found in this study. It was probably because these patients had advanced CKD and had already been under the routine care by their nephrologists.

The limitation in this study is the availability of laboratory data. To illustrate, since our patients came from all over the country to be registered on the kidney transplant waiting list, they were treated for their renal disease in other hospitals and laboratory monitoring was done there. This led to considerable uncertainty regarding the availability of their data. DRPs could not be assessed in patients with missing laboratory data. A number of patients had missing parathyroid hormone values so the prevalence of DRPs related to the management of parathyroid hormone metabolism disorders estimated in this study was the minimum possible amount. When questioned about the reasons why parathyroid hormone values was missing, some cases forgot to bring the laboratory reports to the pre-KT evaluation appointment, some patients could not get the parathyroid hormone test because they were unable to afford it, and some doctors ordered this test less frequently than recommended by the guideline that may be due to their personal opinion of cost-effectiveness, patient's clinical condition, and difficulties in laboratory testing.

This study points out that noncompliance to drug therapy was the main cause of DRPs in this setting and these are preventable. Therefore, there is a need for further study to investigate methods to reduce noncompliance.

In conclusion, we have found that CKD-MBD related DRPs occurred in about two-thirds of ESRD patients awaiting renal transplantation. Noncompliance to drug therapy was the most common type identified. Calcium salts were the most frequent medicine involved. These manageable DRPs are a burden on the healthcare system to pay attention to control them in order to avoid potential problems after transplantation. The inclusion of pharmacists in the multidisciplinary team to provide repeated essential information about individualized medication usage may help to improve chronic care and prevent DRPs in these patients.

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