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Pharmacist's Role in Deprescribing Medications in An Adult with End-Stage Kidney Disease

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Abstract

Purpose: Individuals diagnosed with End-Stage Kidney Disease (ESKD) have multiple comorbidities and require many medications. Alterations in renal function, coupled with pharmacokinetic and pharmacodynamic changes in individuals with increasing age, can result in adverse drug effects. The purpose of this case is to demonstrate how interventions recommended by a clinical pharmacist improved medication safety for a patient with ESKD.

Case: A 55-year-old male with a past medical history of ESKD, peripheral artery disease, chronic heart failure, cirrhosis, and major depressive disorder had a clinical pharmacist-led medication review. During the review, the clinical pharmacist identified several medications (i.e., bumetanide, metolazone, spironolactone, rivaroxaban) that should be discontinued since the patient had no urinary flow output and was on dialysis. Before the recommendations were addressed, the patient experienced retinal hemorrhaging, which may have been a rivaroxaban-associated adverse drug reaction. After addressing the retinal hemorrhaging, the physician discontinued the rivaroxaban and initiated clopidogrel. Additionally, both bumetanide and metolazone were discontinued.

Conclusion: This case demonstrates that clinical pharmacists can have a significant role in medication therapy management and medication safety, especially in patients with ESKD. Healthcare providers with patients with ESKD on dialysis can greatly benefit from consulting with a clinical pharmacist who can evaluate all medications for safety and efficacy.

Keywords: Pharmacotherapy • Medication therapy management • Bumetanide • Metolazone • Spironolactone • Rivaroxaban • End-stage kidney disease • Dialysis

Abbreviations: ESKD: End-Stage Kidney Disease • PAD: Peripheral Artery Disease • CHF: Chronic Heart Failure • PCP: Primary Care Physician • FDA: United States Food and Drug Administration • PK: Pharmacokinetic • PD: Pharmacodynamic • CrCl: Creatinine Clearance • CKD: Chronic Kidney Disease

Introduction

End-Stage Kidney Disease (ESKD) has a prevalence of approximately 2,000 patients per million in the United States [1]. Patients are diagnosed with ESKD when they present with a glomerular filtration rate <15 mL/min per 1.73 m^2 or if they require dialysis [2]. Reduced glomerular filtration rate results in increased accumulation of many drugs and active or toxic metabolites [3]. This requires dosage adjustments for many medications and, in some cases, results in contraindications [3]. Additionally, the physiologic changes that occur as a result of aging can influence the Pharmacokinetics (PK) and Pharmacodynamics (PD) of various medications [4]. These changes include reduced distribution, metabolism, and elimination, all of which can increase serum concentrations for certain medications [4].

Often, individuals diagnosed with ESKD have multiple comorbidities and require many medications, which can result in polypharmacy (i.e., the prescribing of excessive or unnecessary medications) [5]. Polypharmacy, coupled with the physiologic changes seen in aging, can lead to inappropriate medication use, adverse drug events, and drug-drug interactions. One solution to ensure safe and appropriate medication use in patients with ESKD is routine medication reviews. These reviews typically confirm medication lists are current and accurate; review safety, efficacy, and appropriateness of the regimen; and develop treatment goals that are patient-centric. This case report presents an example of how a medication review, led by a clinical pharmacist, identified inappropriate medications for a patient with ESKD.

Case Presentation

A 55-year-old male with a past medical history of ESKD (creatinine clearance (CrCl) ~ 15 mL/min) receiving dialysis three times weekly, Peripheral Artery Disease (PAD), Chronic Heart Failure (CHF), cirrhosis, gait instability, right/left transmetatarsal amputations, and an amputation below the knee of the right leg, presents to his new Primary Care Physician (PCP) as a new enrollee to the Program of All-Inclusive Care for the Elderly (PACE). The patient's medical history and medication regimen is presented in Table 1. Upon enrollment, the physician requested the clinical pharmacist to perform a medication review to optimize the patient's complex medication regimen. The clinical pharmacist identified several medications with unknown efficacy due to the patient's kidney function and urine output: bumetanide, metolazone, spironolactone, rivaroxaban, and atorvastatin. Bumetanide, metolazone, and spironolactone are all contraindicated in patients with anuria; therefore, the clinical pharmacist recommended discontinuing these medications upon learning that the patient's urine output was absent. The pharmacist also recommended discontinuing the

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Table 1. Past medical history and comprehensive list of patient's medications at initial presentation.

Indications	Medications
Chronic Anemia	**Ferrous sulfate 325 mg:** Take 1 tablet by mouth once daily
Chronic Heart Failure	**Bumetanide:** Take 1 tablet by mouth twice daily for fluid retention
	Carvedilol 6.25 mg: Take 1 tablet by mouth twice daily
	Metolazone 5 mg: Take 1 tablet by mouth once daily half an hour prior to bumetanide
	Spironolactone 25 mg: Take 1 tablet by mouth 3 times weekly on M/W/F for fluid retention
Chronic Obstructive Pulmonary Disease	**Budesonide/formoterol 160-4.5 mcg/actuation:** Inhale 2 puffs by mouth twice daily
Constipation	**Polyethylene glycol 3350 17 g/dose powder:** Dissolve 17 g in 4oz of fluid and drink once daily
	Sennosides/docusate 8.6-50 mg: Take 1 tablet by mouth twice daily
End-Stage Kidney Disease	**Sevelamer carbonate 800 mg:** Take 3 tablets by mouth 3 times daily with meals
Gastroesophageal reflux disease	**Pantoprazole 20 mg:** Take 1 tablet by mouth every 5 minutes (max 3 doses) as needed
Hyperlipidemia	**Atorvastatin 40 mg:** Take 1 tablet by mouth at bedtime
Insomnia	**Melatonin 3 mg:** Take 1 tablet by mouth once daily at bedtime
Major Depressive Disorder	**Bupropion HCL 150 mg SR:** Take 1 tablet by mouth twice daily
	Citalopram 20 mg: Take 1 tablet by mouth once daily
Peripheral Artery Disease	**Rivaroxaban 2.5 mg:** Take 1 tablet by mouth twice daily
Peripheral Neuropathy	**APAP 650 mg ER:** Take 1 tablet by mouth 3 times daily
	Gabapentin 100 mg: Take 1 capsule by mouth twice daily
Pruritis	**Betamethasone cream 0.1%:** Apply cream topically two times a day to the navel
Vitamin Supplementation	**Cholecalciferol 1,000 unit:** Take 1 tablet by mouth twice daily
	Folic Acid 8000 mcg: Take 1 tablet by mouth once daily
	Folic Acid/vitamin B complex and vitamin C 0.8 mg: Take 1 tablet by mouth daily

patient's anticoagulant, rivaroxaban, due to the safety concern in patients with ESKD. This patient is also at increased risk for falls due to a history of gait instability post-amputation, and anticoagulant use may increase his risk for bleeding. Prior to discussing the recommendations, the PCP provided the clinical pharmacist with an update, stating the patient reported a new onset of blurry vision and "seeing red." Upon further examination, it was noted that the patient had a pre-retinal and vitreous hemorrhage of the left eye. The etiology of this complication is unknown; however, such reactions have been documented with rivaroxaban use. During follow-up with the PCP, the decision to discontinue rivaroxaban was made and clopidogrel 75 mg once daily was initiated for PAD. Additionally, the PCP agreed to discontinue metolazone and bumetanide since there was minimal urine production noted. The PCP decided to continue the spironolactone for cardiovascular benefits and to continue to monitor potassium levels.

Approximately three months after the medication changes were implemented, the patient's edema was managed appropriately with the scheduled dialysis, and there were no additional reported adverse drug events or complications. Although the patient still reported blurred vision, he was considered clinically stable, and his gait continued to improve. During a follow up patient review, atorvastatin was discontinued due to the patient's declining clinical status.

Discussion

Considering the mechanism of action and the patient's progressive kidney disease, all three diuretics (i.e., bumetanide, metolazone, and spironolactone) required reassessment. Bumetanide is a loop diuretic which targets the Na-K-Cl co-transporter at the thick ascending loop [6]. Metolazone is a thiazide-like diuretic which targets the Na-Cl co-transporter at the early distal convoluted tubule [6]. Finally, spironolactone is a potassium-sparing diuretic which targets the mineralocorticoid receptors in the late distal convoluted tubule [6]. Unlike spironolactone, both bumetanide and metolazone can still be used in patients with declining kidney function [7,8]. However, bumetanide or metolazone should not be used when there is a lack of urine output [7].

In our patient, bumetanide and metolazone were indicated for the treatment of edema as a result of CHF. The addition of spironolactone in this case was likely used to increase the effectiveness of the two proximally acting diuretics, bumetanide and metolazone [9]. In addition, spironolactone was prescribed for this patient likely because it has demonstrated morbidity and mortality risk reduction benefit in CHF management [10,11]. After the clinical pharmacist learned the patient was not producing urine, bumetanide and metolazone were determined to be contraindicated, and the continued use of both medications in the state of anuresis would increase the patient's risk for severe electrolyte imbalances. As such, both medications were discontinued in this patient; however, spironolactone was continued. While evidence demonstrates cardiovascular benefits with regular dosing of spironolactone, it is unknown if the cardiovascular benefits of spironolactone are evident with the current dosing of 25 mg three times weekly and this requires further investigation [12]. Of note, spironolactone can increase the risk for hyperkalemia, especially in patients with ESKD [8]; however, one study noted that hyperkalemia risk was not increased when using a three times a week dosing strategy [12]. Regardless, patients continuing spironolactone while on dialysis should have their potassium levels closely monitored.

Rivaroxaban, a selective inhibitor of Factor Xa, was prescribed for PAD. This medication inhibits free factor Xa and prothrombinase activity, which inhibits platelet aggregation by decreasing thrombin generation [13]. It has several United States Food and Drug Administration (FDA) approved indications, including reduction in risk of major cardiovascular events for patients with PAD [13]. Although the appropriate FDA-approved dosing was prescribed for PAD (i.e., rivaroxaban 2.5mg twice daily), guidelines recommend that rivaroxaban should be used in combination with either aspirin or clopidogrel when used for PAD [14]. Because rivaroxaban is not dialyzable, exposure to rivaroxaban is expected to be higher in patients on dialysis, thereby increasing the risk for bleeding [13]. It is also important to note that the use of rivaroxaban 2.5 mg twice daily has not been studied in patients with advanced chronic kidney disease [(CKD); CrCl <30 mL/min] [14]. At the time of this publication, a randomized control trial (NCT03969953) is investigating the efficacy of low-dose rivaroxaban in this patient population, which may provide clearer recommendations [15]. Based on this information and unclear evidence, the decision to discontinue rivaroxaban was made. Consequently, the delay in implementing the recommendation may have contributed to the development of retinal/vitreous hemorrhage. Although this correlation cannot be confirmed, there have been reported cases of hemorrhaging in the eye for several anticoagulants including rivaroxaban [16]. Following discontinuation of rivaroxaban, clopidogrel was initiated; clopidogrel is FDA-approved to reduce the rate of myocardial infarction and stroke in patients with established PAD and does not require renal dose adjustments [17].

As mentioned, atorvastatin was also discontinued upon follow-up due to the patient's declining clinical status. Evidence indicates significant cardiovascular benefit with the use of statins in individuals up to the age of 75 [18,19]. However, in individuals with declining health status or complex comorbidities, the benefits of continuing preventive medications, such as statins, can be outweighed by risks [18,19]. In such cases the statins should be discontinued [18,19].

In addition to recommendations regarding the patient's renal function, the pharmacist made other recommendations for medication safety. Concerns included a drug-drug interaction between bupropion and citalopram resulting in increased concentrations of citalopram [20]. Bupropion is a strong substrate of the cytochrome P450 (CYP) 2D6 enzyme, which results in increased concentrations of CYP2D6 substrates [20]. Since citalopram is partially metabolized by CYP2D6, increased concentrations of citalopram may increase the risk for adverse drug events such as serotonin syndrome [21,22]. Furthermore, the active metabolite of citalopram, desmethylcitalopram, is mostly excreted through metabolism by CYP2D6. Significant accumulation of the metabolite is therefore expected when citalopram is coadministered with bupropion. Manufacturer guidance for bupropion indicates that it should be used with caution in patients with reduced kidney function and avoided in patients with CrCl <15. Finally, both citalopram and bupropion are associated with significant block of the rapid component of the delayed rectifier potassium current (IKr; hErRG) and with an increased risk of drug-induced Long QT Syndrome [23,24]. Therefore, a recommendation for tapering bupropion's frequency from twice daily to once daily dosing was made and transitioning the patient from citalopram to another selective serotonin reuptake inhibitor is being considered [25].

There is evidence which describes the prevalence of potentially inappropriate medications in adults with CKD regardless of the CKD stage [26]. Additionally, there have been multiple studies and reports of pharmacist-led collaborative practices to address medication appropriateness for patients on dialysis [27-29]. In one study, a team of clinical pharmacists was able to promote safe medication use by reducing polypharmacy, anticholinergic burden, and central nervous system-acting medications [30,31]. Another study evaluated pharmacist-led medication reviews in pre-dialysis and dialysis patients and the acceptance rate of recommendations by nephrologists [29]. Of the 120 patients reviewed, 100 patients were identified with a total of 277 medication discrepancies; these were defined by medication differences between pharmacy records and hospital medication lists [29]. The study also identified 115 patients with 422 instances of inappropriate drug/dose and 46 patients who could benefit from medication counselling [29]. In an observational cross-sectional study of Medicare-enrolled Medication Therapy Management-eligible patients, rates of potentially inappropriately prescribed medications increased with the decline of kidney function [32]. Patients with stages 4 and 5 CKD were found to have 11 times the odds of one potentially inappropriately prescribed medication compared to CKD stage 3 patients [32].

In general, pharmacists can play a critical role in identifying drug and dose appropriateness, especially when kidney function declines. There is no standard approach/model for provision of medication management to patients on dialysis. One summary article provided guidance on recommendations for this theoretical model: medication management services should be implemented within the dialysis facility, medication reconciliations should be performed before medication reviews and this service should be consistently coordinated with other care providers both inside and outside the facility [28]. The medication reviews in the proposed model would be performed by a pharmacist or by healthcare workers trained by a pharmacist, with the goal that a trained clinician would provide consistency in their quality of medication reviews [28]. Within our practice, a clinical pharmacist assesses and periodically reassesses all medications for safety and efficacy, which frequently involves adjusting renal doses and discontinuing potentially inappropriate medications [33]. This collaborative involvement becomes especially important when caring for patients with ESKD on dialysis.

Conclusion

This case demonstrated the role clinical pharmacists can play in the management of adults with ESKD on dialysis. ESKD greatly increases the risk for adverse medication-related events due to decreased clearance of drugs, resulting in increased drug concentrations. A clinical pharmacist can improve medication safety and efficacy through the services they provide for these patients.

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