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Case Study

Urinary Tract Infection in Chronic Renal Insufficiency: A Case Study

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ABSTRACT

Inappropriate use of drugs in patients with renal impairment may be harmful and may have deleterious effects on health outcomes. A case of 75 year old female patient with systemic hypertension, type 2 diabetes mellitus, chronic renal failure and urinary tract infection has been discussed. Both fasting and random blood sugar levels were elevated. Laboratory data showed increase in serum urea and creatinine levels. Urine culture and sensitivity study showed the presence of *Escherichia coli* and was found to be sensitive to amikacin, cefepime, meropenem and nitrofurantoin. On the day of admission, the patient was in end stage renal disease as her calculated glomerular filtration rate was 11.3ml/minute. Modified Diet for Renal Disease equation was used to calculate glomerular filtration rate and dose adjustments were made accordingly. Drugs prescribed include glipizide 2.5 mg, sulbactum 1 g , pantoprazole 40 mg, paracetamol 650 mg, prulifloxacin 600 mg, sodium citrate 10 ml, fexofenadine 60 mg, balofloxacin 100 mg, hyoscine 20 mg, domperidone 10 mg, ciprofloxacin 500 mg, ramipril 5 mg and lactulose 10 ml. A systematic medication chart review revealed that ciprofloxacin is the drug of choice with altered dose recommendations for the case of interest while prulifloxacin and balofloxacin has to be used with caution in severe renal insufficiency. Either reduced dose or increased dosing interval is necessary for ciprofloxacin and ramipril in the selected patient. Also, the review has documented other drug related problems such as major drug-drug interaction of fluoroquinolones with glipizide and therapeutic duplication of fluoroquinolones. This case study serves as a potential source of information for the management of urinary tract infection in patients with chronic renal insufficiency.

Key words: Urinary tract infections, Drug related problems, Glomerular filtration rate, Chronic renal failure.

1. INTRODUCTION

Kidney disease is increasingly recognized as a significant health issue, mostly affecting elderly people. Pharmacokinetics of renally eliminated drugs is significantly altered and drug dosage adjustments based on individual renal function maximizes

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therapeutic efficacy and minimizes ADRs in such patients. Moreover, drug related problems in renal impairment can potentially interfere with desired health outcomes [1]. The objective of the case study are to assess the incidence of Drug Related Problems (DRP) and inappropriate dosing of renally cleared drugs in a hospitalized patient with renal impairment and to understand the opportunities for reactive interventions on various drug related issues for the selected patient.

2. MATERIALS & METHODS

Demographic data, past medical history, laboratory data and prescribed drugs were recorded in a customized data entry form. The severity of renal insufficiency was determined by calculating the patient's GFR using Modified Diet for Renal Disease (MDRD) equation as follows:

$$GFR = 186.3(\text{serum creatinine})^{-1.154} * (\text{age})^{-0.203} * 0.742(\text{Female})$$

Whenever follow up serum creatinine was measured for the patient, GFR was estimated and dose requirements were calculated once again. A systematic medication chart review was also performed in order to understand the incidence of various DRPs such as drug duplication, underdosing, overdosing, drug interactions, adverse drug reactions and other medication errors.

3. RESULTS AND DISCUSSIONS

A female patient of age 75 years admitted in the General Medicine department for 9 days with chief complaints of abdominal pain, vomiting and decreased urine output has been discussed. She was a known case of type 2 diabetes mellitus, systemic hypertension and chronic renal failure. Patient's laboratory results showed that the temperature was elevated for the first two days, mean blood pressure was 130/80 mmHg and pulse was 80 beats/ minute. Blood counts were normal with elevated total leucocyte count and erythrocyte sedimentation rate. Renal function test showed elevated serum urea and creatinine levels of 55 mg/dl and 4.1mg/dl respectively on the day of admission. Urine culture and sensitivity test showed the isolates of *Escherichia coli* at 10,000 CFU/ml and it was found to be sensitive to amikacin, meropenem, nitrofurantoin and cefepime. With the above subjective and objective data patient was diagnosed to have type 2 diabetes mellitus, systemic hypertension, chronic renal failure and urinary tract infection.

Following are the drugs prescribed to the patient:

Drug prescribed	Dose	Frequency	D1	D2	D3	D4	D5	D6	D7	D8	D9
Tab. Glipizide	2.5 mg	BD	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inj. Sulbactum	1 g	OD	✓	✓	✓	✓	✓	✓	-	-	-
Inj. Pantoprazole	40 mg	OD	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tab. Paracetamol	650 mg	OD	✓	✓	✓	✓	✓	✓	✓	-	-
Tab. Prulifloxacin	600 mg	OD	✓	✓	✓	✓	✓	✓	-	-	-
Syr. Sodium citrate	10 ml	TID	✓	✓	✓	✓	✓	✓	✓	✓	-
Tab. Fexofenadine	60 mg	BD	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tab. Balofloxacin	100 mg	BD	-	-	-	-	-	-	-	✓	✓
Inj. Hyoscine	20 mg	BD	-	-	-	-	-	-	-	✓	✓
Tab. Domperidone	10 mg	OD	-	-	-	-	-	✓	✓	✓	✓
Inj. Ciprofloxacin	500 mg	BD	-	-	-	-	-	✓	✓	✓	✓
Syr. Lactulose	10 ml	HS	-	-	-	-	✓	✓	✓	✓	✓
Tab. Ramipril	5 mg	BD	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tab. Multivitamin		OD	✓	✓	✓	✓	✓	✓	✓	✓	✓

The kidneys have important physiological functions and have a major role in excretion of drugs. Chronic kidney disease (CKD) is defined as the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) for three months or longer [2]. The degree of renal insufficiency and the severity of kidney disease are generally reflected in the reduction of GFR. The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) established a classification of CKD that has been accepted and used worldwide [3].

Table 1: Chronic Kidney Disease Staging [4]

Stage	Description	GFR (ml per minute per 1.73 m^2)
1	Kidney damage with normal or	≥ 90

	increased GFR	
2	Kidney damage with a mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	End Stage Renal Disease	< 15 (or dialysis)

Diabetes (30%) and Systemic hypertension (20%) account for the major cause of CKD [5]. The most commonly used formula for calculating GFR are the Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease equation (MDRD) [6,7].

Though MDRD equation was derived from a study population of 1,628 men and women with CKD, aged from 18 to 70, predominantly Caucasian, nondiabetic, and who were non-kidney-transplant recipients [8] , many studies show that MDRD equation is suitable for use across populations with CKD [9,10, 11].

In clinical practice, few patients have their weights taken regularly which in turn limits the use of Cockcroft-Gault equation in attempts to obtain more detailed information about the renal function whereas MDRD equation is based on more easily available information such as gender, age and serum creatinine levels. Hence it was the preferred method in the current study. Patient's GFR was calculated to be 11.3 ml/min.

Dosing considerations are important in this patient because of two main reasons: Uremia in chronic renal failure reduces glomerular filtration and/or active secretion, leading to a decrease in renal drug excretion resulting in a longer elimination half-life of the administered drug. A declining renal function leads to disturbances in electrolyte and fluid balance, resulting in physiologic and metabolic changes that may alter the pharmacokinetics and pharmacodynamics of a drug [12]. Therapeutic and toxic responses may be altered due to changes in drug sensitivity at the receptor site. Secondly, patient is 75 years of age, considered to be a geriatric. As age progresses the normal function of kidney declines owing to the structural and vascular changes occurring to the kidney such as reduced renal mass, number of glomeruli and renal blood flow [13]. Therefore drug dose adjustment is critically important in these patients.

A detailed medication chart review revealed that prulifloxacin and sulbactum were used to treat UTI in the patient though the isolated *Escherichia coli* from the patient's urine sample were sensitive to nitrofurantoin, meropenem, amikacin and cefepime. This may be due to the following reasons: Nitrofurantoin is contraindicated in patients with GFR <60 ml/min due to nitrofurantoin toxicity. Nitrofurantoin has a toxic metabolite that can accumulate in patients with chronic kidney disease, causing peripheral neuritis [14]. Meropenem has to be used with caution in renal failure patients and dose adjustments have to be done based on GFR. Amikacin has the risk of developing ototoxicity and nephrotoxicity in a geriatric patient with renal failure. Kidney function, serial audiogram and vestibular function in those with pre-existing renal impairment has to be monitored. If used, initial doses should be based on an accurate GFR estimate. Renal function and drug concentrations should be monitored and dosages adjusted accordingly. Cefepime has to be used with caution in elderly patients with renal failure as it has the risk of developing life threatening encephalopathy and seizure [15]. In such cases constant monitoring of kidney function and dose adjustments are necessary.

Urinary tract infection caused by *Escherichia coli* could be treated with trimethoprim–sulphamethoxazole fixed dose combination or fluoroquinolones. But use of trimethoprim is contraindicated in patients with a GFR < 15 ml/min. Fluoroquinolones are the drug of choice for the treatment of UTI in patients with renal dysfunction [16]. In the present case, therapy was started with prulifloxacin 600 mg, a newer generation fluoroquinolone, for the first 6 days and later shifted to

balofloxacin 100 mg, another newer generation fluoroquinolone. However sufficient data are not available in literature to prove the safety of these two drugs in renal impairment. Ciprofloxacin was added to the patient's pharmacotherapy from 6th day. Literatures reveal that ciprofloxacin is eliminated in the urine to a greater extent (fraction excreted unchanged, f_u = 0.7). It is filtered as well as secreted in the glomeruli and has good tissue penetration. As the concentration of ciprofloxacin in urine after 24 hours remained above the minimum inhibitory concentration for most urinary pathogens, it appears to be the preferred fluoroquinolone in CRF [17]. Such strong evidences are deficient in case of prulifloxacin and balofloxacin prescribed in the present case. The prescribed dose of injection ciprofloxacin was 500 mg BD, while the recommended dose is 400 mg OD for a patient with GFR less than or equal to 30 ml/min. Also, oral ciprofloxacin at a dose of 250-500 mg for every 18 hours for uncomplicated UTI depending on severity has also been recommended [18].

Therapeutic duplication of fluoroquinolones observed in the selected case leads to an increased risk of side effects of the particular drug. For a hypertensive patient with renal impairment, recommended initial dose of ramipril is 1.25 mg once daily with dose titration until blood pressure is controlled and the maximum dose per day should not exceed 5 mg [19]. But the subject of interest received an overdose of 5 mg twice daily. Literature suggests that ramipril has to be used with caution as it increases serum creatinine and urea in renal failure patient; hence dose reduction is required [20]. Another drug related issue observed in this case was the possibility of major drug-drug interaction between glipizide and fluoroquinolones which may lead to either hyperglycemia or hypoglycaemia. Monitoring of blood glucose levels is recommended when these agents are given together.

4. CONCLUSION

A case with multiple co-morbidities of diabetes mellitus, hypertension, chronic renal failure and urinary tract infection has been discussed. Though bacterial sensitivity studies provide initial guidelines on drug choice, patients with CRF have reduced filtering ability; hence treating UTI in such patients require careful selection of drugs in order to avoid drug accumulation and toxicity. Fluoroquinolones appear to be the drug of choice for treating UTI in patients with renal dysfunction after appropriate dose reduction. More evidences are necessary for the safe use of newer generation fluoroquinolones such as prulifloxacin and balofloxacin in renally impaired patients. Also, management of UTI in patients with CRF has attained little or no attention. Hence, the case presented here is a valuable source of information that can lead to vital research. DRPs necessitating heightened vigilance, prudent management and also providing opportunities for reactive interventions by the pharmacist have also been discussed. However, more such cases are to be documented to bring forth evidence to incorporate pharmacist in the healthcare team in order to improve current pharmacotherapy.

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