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Drug Related Problems in Chronic Kidney Disease: A Brief Review

Abhishek Pradhan[1], Ambika V[2], A R Shabaraya[3], Chinju Jose[1], Niveditha TV[1], Shwetha N[1]

[1]Asst. Professor, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka, India – 574143.
[2]Student, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka, India – 574143.
[3]Professor & Head, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, Karnataka, India – 574143

Corresponding Author: Ambika V

ABSTRACT

Drug Related Problems (DRPs), also known as Medication Related Problems or MRPs, are the events which occur due to the drugs used for treatment, which actually or potentially interfere with the desired therapeutic outcome. Actual DRPs are those which are actually observed in the patient whereas potential DRPs are those which may develop if appropriate interventions are not met. Chronic Kidney Disease (CKD) can be defined as abnormalities in the kidney structure or function which is present for at least 3 months and has some impact on the health of the individual affected. CKD patients are said to be at high risk for DRPs due to polypharmacy and moreover, due to their impaired renal excretion. In these patients, DRPs can cause decreased quality of life, increased length of hospital stay, increased health-care cost, and may even increase the risk of morbidity and mortality.

It is considered that the necessity of dose adjustment or drug avoidance in patients with kidney disease is probably under-estimated in clinical practice. This article focuses on the review of published articles on drug related problems in patients with chronic kidney disease. The aim of this review is to improve the understanding regarding the prevalence, risk factors, identification, classification, etiology and the role of pharmacist in the management of DRPs in CKD patients.

Key words: Drug Related Problems, Chronic Kidney Disease, Pharmaceutical Care

INTRODUCTION

Chronic kidney disease (CKD) can be defined as abnormalities in the structure or function of the kidney, which is present for a period of at least 3 months, with negative impact on the health. CKD is one of the health problems which calls for early detection and treatment to slow down the progression of the disease due to the fact that the prognosis turns graver as the disease advances. It is often associated with an increase in morbidity, mortality, and cost of health care for individual patients as well as the health care systems. The global prevalence of CKD is estimated to be around 11%-13%.

Drug related problems (DRPs) are events involving drug therapy that become actually or potentially harmful to a patient's health or which prevent patients from optimally benefiting from the treatment. [1] Medication errors and adverse drug reactions (ADRs) are found to be the most common form of DRPs. Hospitalized patients are found to be more prone to the occurrence of DRPs which are reflected by longer duration of hospital stays and thus increased health-care costs. Awareness regarding DRPs may help in identifying, resolving, and preventing potential DRPs and is a prerequisite for better patient care. [2] It can also help in significantly decreasing the additional cost burden for the

patient's side which are brought about by the DRPs.

Among patients with CKD, the prevalence of DRPs has been estimated to be 2.8 (95% confidence interval [CI] = 2.3-3.2) DRPs/ patient for creatinine clearance 30-59 mL/min4; and 4-8 DRPs per patient on hemodialysis. [3] Therefore it is safe to say that DRPs are commonly seen in patients who have renal insufficiency and those who are on hemodialysis. Factors associated with DRPs in these patients are found to be: presence of more than 3 comorbid conditions; change in drug therapy 4 or more times in the past 12 months; 5 or more drugs in current drug regimen; 12 or more doses of medication per day and inclusion of drugs that call for therapeutic monitoring. Almost all CKD patients are at risk for DRPs owing to the presence of multiple risk factors. Furthermore, these patients are usually found to be non-adherent to their medications. It has been demonstrated that the incidence of DRPs and adverse drug events (ADEs) is higher in patients with CKD than in those without any sort of renal insufficiency. [4]

This review aims to enhance the understanding regarding the prevalence, risk factors, identification, classification, etiology and the role of pharmacist in the management of DRPs in CKD patients.

DISCUSSION

Prevalence:

Drug related problems (DRPs) are very common in patients with chronic kidney disease (CKD). More than 80% of patients with CKD experience one or more drug related problem. [1], [2], [5], [6]. In a study conducted in Kenya, an average of 4.5 DRPs was identified among 60 participants and each of these 60 participants had at least one DRP thus resulting in a prevalence rate of 100%. [7]. Thus it can be safely assumed that the prevalence of DRPs in CKD patients is quite high.

The leading causes of DRPs are found to be drugs used in the management of cardiovascular disorders as well as drugs acting on the gastrointestinal system. [1], [3], [6], [8], [9]. Antibiotics and diuretics are found to be the other classes of drugs which are commonly associated with DRPs in CKD patients. [3], [4], [8].

Risk Factors:

Only one of the studies included in this review focused on risk factors associated with DRPs in CKD patients. In the study conducted by Garedow et al., in Jimma, Ethiopia, it was found that patients on 5 or more medications were 4.695 times more likely to have DRPs than the patients who took less than 5 drugs. Similarly, the patients who had 5 or more comorbidities were 3.616 times more likely to develop DRPs compared to those who had less than 5 comorbidities. They also found that patients in stage V CKD were 3.941 times more likely to have DRPs compared to those in other stages of CKD. [1] Hence polypharmacy, presence of comorbidities, and stage V of CKD are found to be independent risk factors for DRPs in CKD patients.

Identification, Assessment and Classification:

The identification and classification of the various drug related problems is usually done with the help of certain guidelines and tools. The various classification systems used for this purpose include American Society of Hospital Pharmacists (ASHP) Systems, Cipolle *et al.*, Granada consensus, Helper/Strand, Pharmaceutical Care Network Europe (PCNE) classification, Problem-Intervention Documentation (PI-Doc) and Westerlund classification.[10] Various versions of the Pharmaceutical Care Network Europe (PCNE) scale are frequently used in for the classification of DRPs. [2], [8], [11], [12]

In a study conducted in Quebec, Canada, the Pharmacotherapy Assessment in Chronic Renal Disease (PAIR) criteria was used to assess medication safety and use issues in patients with CKD. [3]. The

PAIR criteria was developed and validated by Desrochers JF, et al. in 2011. [13] In this study, the severity of the identified DRPs was assessed using the Severity Categorization for Pharmaceutical Evaluation (SCOPE) criteria. According to SCOPE criteria, severity is determined by the intensity of the pharmaceutical intervention required to manage the DRP. These criteria suggest 3 levels of severity (mild, moderate, and severe) with two levels of interventions per category. Level I interventions (mild severity) consist of preventing a DRP through educating the patient or by the transmitting of relevant clinical information to the clinician. At level II (mild severity), a pharmaceutical opinion may be issued to the treating physician, which is required to resolve a DRP. It may be about the patient's medication history or the therapeutic value of a prescribed treatment. The pharmaceutical opinion is a reasoned assessment, given under the pharmacist's legal authority. At level III (moderate severity), pharmacists implements specific monitoring and creates a follow-up plan to manage a DRP. When a DRP is more severe, patients may need to be referred to their physician as soon as possible (at level IV, moderate); need to be referred immediately to the emergency room or to their physician (at level V, severe); or require immediate assistance (at level VI, severe). [3]

In a study conducted in France by Belaiche S, a sophisticated pharmacist intervention tool called ACT-IP which was developed by the French Society of Clinical Pharmacists in 2003 was used. This tool includes a pharmaceutical intervention (PI) report form and tables to assist codification. The report form gathers the following information through check boxes: medical characteristics of the patient, type of hospital service, identification of DRPs, type of PI and identification of the drug involved in the PI. All PIs are entered into the Act-IP database on the SFPC website. [6]

Types of Drug Related Problems:

a. Adverse Drug Reactions:

Adverse drug reactions or ADRs can be defined as unpredictable, undesirable, untoward effects caused by the medication. World Health Organization (WHO) defines ADRs as "A response to drugs which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function". [5]

ADRs can occur at normal doses of the drug given for the normal indications. The causes of ADRs are broadly divided into non-allergenic and allergenic and can be further subdivided into incorrect administration of the drug, administration of an unsafe drug, a drug reaction or an allergic reaction. [7]

The majority of ADRs seem to be caused by anticoagulant drugs, with heparin, enoxaparin and warfarin being the most implicated medications. [14] ADRs, specifically non-allergic ADRs, contribute to around 39% of the all the DRPs in CKD patients. [8]

Various scales can be used to assess ADRs. The Naranjo scale is a widely used tool to assess the causality related to the drug. The scale consists of a series of 10 questions that are answered as either "Yes", "No", or "Do not know". Different points (-1, 0, +1 or +2) are assigned to each answer. Based on the total number of points the probability of occurrence ADRs is scored as definite, probable, possible or doubtful. [15] The Naranjo algorithm is said to be simpler and less time-consuming compared to other scales like the Kramer algorithm and hence is used more commonly. [16]

b. Drug Interactions:

In clinical practice, different drugs are often combined for the treatment of patients with chronic kidney disease. This may produce drug interactions (DI) with intentional beneficial effects, but in some cases undesired outcomes can also occur. These undesired outcomes include ineffective treatment and severe adverse

events. Drug-drug interactions can be defined as "the set of alterations introduced upon the therapeutic effect of a given drug stemming from the co-administration of one or more medications". In this context, drug interactions appear as the cause of a drug-related problem (DRP) which, when present, negatively impacts the morbidity, mortality, length of hospitalization, quality of life, and cost of care. [17] Drug interactions may be actual or potential.

The risk factors for potential DDIs are found to be age less than 60 years, number of prescribed medicines more than or equal to 5, hypertension, and the lengthy hospitalization of patients. [18]

The number of medications and hypertension can be considered as significant and independent predictors of DDIs. As the prevalence of DDIs is high among CKD patients, it calls for careful monitoring of drug therapy. [19]

c. Improper Dosing and Choice of Drug:

Literature has often pointed out that errors in dosing are one of the leading causes of DRPs in patients with CKD. [1], [2], [6], [11] Impaired renal function has pronounced effects on the pharmacokinetic properties of many drugs. The most common effect is a decrease in drug excretion, resulting in an increase in plasma concentrations and increased risk of drug toxicity. Therefore, there is an increased risk of DRPs such as the use of drugs which are contraindicated and use of inappropriate dosages, with potentially adverse outcomes. Thus in CKD patients, it is essential to select the appropriate drug and individualize the dosage in order to avoid the occurrence of adverse drug reaction (ADR). [22]

Drug dosing errors are common in patients with CKD and can cause numerous adverse effects and result in poor health outcomes. Dosages of drugs cleared by the kidneys should be adjusted according to creatinine clearance or glomerular filtration rate and the dose should be calculated using online or electronic calculators. Recommended methods for the adjustment of maintenance dose are reduction of dose, lengthening of the dosing interval, or both. Both physicians and pharmacists should be familiar with commonly used medications that require dosage adjustments. [21]

GR Matzke *et al*., proposed a step wise approach to adjust drug dosage regimen for patients with CKD and acute kidney injury (AKI). [22]

Step 1: Obtain history and relevant demographic/clinical information.
Step 2: Estimate GFR
Step 3: Review current medication
Step 4: Calculate individualized treatment regimen
Step 5: Monitor for drug response and toxicity
Step 6: Revise regimen based on response

Ambulatory antibiotic dosing errors are exceedingly common in CKD patients. Strategies which include but not limited to eGFR reporting are needed to prevent these medical errors. [23]

In a study conducted in Pakistan, a total of 205 medical charts were assessed. Out of the 1534 drugs that were prescribed to CKD patients, nearly 34.0% drugs required dose adjustment. Among these drugs, only 41.8% were properly dose adjusted. [24]

The choice of drug used for treatment also plays an important role in determining if the patient will experience a DRP.

The use of renal risk drugs in patients with RI stages 3, 4 and 5 is seen very commonly. Around 26% of the renal risk drugs are associated with DRPs. The most common drug classes that are associated with DRPs due to improper drug choice are antibacterials, antithrombotic agents, angiotensin-converting enzyme (ACE) inhibitors, opioids and non-steroidal anti-inflammatory drugs (NSAIDs). [25]

Improper drug selection is a major cause of DRPs in patients with renal impairment. [8], [11]

d. Need for Additional Drug Therapy:

In this category of DRPs the patient does not receive a drug for a medical condition despite the need for such a drug. It may also include drugs for prophylaxis.

It is estimated that around 30% of the patients ailing with CKD are assessed to have need for additional drug therapy. [1], [6]

e. Failure to Receive Drug:

It is also classified sometimes as non-adherence. Non-adherence is described as a patient's inability or unwillingness to follow a prescribed drug regimen which is judged to be clinically appropriate, effective and able to produce the desired outcome without harmful effects. It may occur due to various reasons, some of which includes the socio economic status of the patients, failures in the drug distribution or administration, lack of health literacy and disability. [5]

Many studies have reported failure to receive drugs or non-adherence as a leading cause of DRPs. [1], [5], [7]

Role of pharmacist:

Clinical interventions to prevent DRPs can be undertaken at three different levels: at the prescriber level, at the patient level, and at the drug level. [1]

Out of these, informing the prescriber, patient counselling and change in dosage are found to be the most recommended interventions at each level. [11]

Information on renal function is essential for the medication safety in these patients. Therefore, it can be implied that improving monitoring of renal function plays a crucial role in helping to avoid medication-related admissions by aiding the adjustment of the dosage regimen and avoidance of certain medications in patients with impaired renal function. So all pharmacists should have access to renal function data of their patients to prevent the occurrence of such adverse events. [26]

Clinical pharmacy education improves the efficacy and efficiency of management of CKD. Thus, the involvement of clinical pharmacists in the team of health care providers is essential to obtain optimal services. This finding should be considered by the policymakers in all hospitals. [27] Continuous identification and resolution of DRPs by a complete pharmaceutical care team helps to improve the health status and quality of life of patients with CKD and plays a vital role in achieving optimum clinical outcomes. [2]

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