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A Descriptive Analysis of Prescribing Patterns of Drugs in Chronic Kidney Disease Patients on Maintenance Hemodialysis

Authors
Chandel Ritesh Kumar[1], Bhargava Jyotsna[2*], Dadheech Jaya[3]
[1,3]Postgraduate Student, [2]Sr. Professor
Department of Pharmacology, SMS Medical College, Jaipur, Rajasthan, India
*Corresponding Author
Bhargava Jyotsna
Sr. Professor, Department of Pharmacology, SMS Medical College, Jaipur, Rajasthan, India

Abstract
Introduction: *Chronic kidney disease is a global threat to health particularly for developing countries because of its increasing incidence, poor outcome and high cost of treatment. The treatment includes dialysis and renal transplantation. Appropriate drug selection for patients with chronic kidney disease (CKD) is important in order to avoid unwanted drug effects and to ensure optimal patient outcomes. Rational drug prescription is a difficult task in CKD patients. So, present study was planned to know the prescribing pattern of drugs in chronic kidney disease on maintenance hemodialysis at Jaipur, Rajasthan.*
Materials and Methods: *The study was carried out in Department of Pharmacology in association with Department of Nephrology, S.M.S. Medical College & Hospital, Jaipur (Rajasthan) from April 2017 to March 2018. Socio-demographic profile and details of drugs administered were recorded in a predesigned and pretested proforma. Results were expressed as percentages and proportions. Pearson's correlation coefficient (r) was calculated to show correlation between drug-drug interaction and drug per prescription.*
Results: *In the present study, out of160 chronic kidney patients majority were males (75.63%) with mean age of 39.5 ± 13.29 years and 24.37% were females with mean age of 40.41 ± 13.53 years. Co-morbidities were anemia (98.13%), hypertension (95.65%), infections (22.5%) and diabetes mellitus (6.85%). Mean number of drugs per prescription were 7.84 ± 1.40. Majority of prescriptions (86.87%) contained 6 to 9 drugs. Most common drugs prescribed were vitamins and minerals (32%) followed by cardiovascular drugs (21.03%) and hematopoietic drugs (14.58%). Majority of prescription (75.62%) contained 3-5 drug-drug interactions (DDIs) and the number of DDIs increased with increasing number of drugs per prescription (r = 0.2606, p value < 0.001).*
Conclusion: *Certain areas of concern such as polypharmacy, underuse of erythropoietin stimulating agents and calcium free phosphate binders and high incidence of potential DDIs were addressed in the present study. There is a need for exploring these issues in detail through future drug use studies.*
Keywords: *Chronic Kidney Disease, Maintenance Hemodialysis, Prescribing Patterns.*

Introduction

Chronic kidney disease (CKD) is a general term for heterogeneous disorders affecting kidney structure and its function. It is defined as either kidney damage or a decreased glomerular filtration rate of less than 60 mL/min/1.73m^2 for 3

or more months.[1] CKD is a key determinant of poor health outcomes for major non-communicable diseases, and it is a worldwide threat to public health. Estimates of the global burden of the diseases reported that kidney and urinary tract diseases contribute 8,30,000 deaths annually making them the 12th highest cause of death (1.4% of all deaths) and disability-adjusted life years (DALY) in 1,88,67,000, i.e. 17th cause of disability (1% of all DALY).[2]

In India, the prevalence of CKD was observed to be 17.2% and about 6% had stage 3 or above among them. It is more common among males compared to females due to stress, alcoholism, hypertension, diabetes mellitus, smoking and cumulative risk factors of chronic vascular disease (CVD).[3]

Appropriate drug selection for patients with chronic kidney disease (CKD) is important in order to avoid unwanted drug effects and to ensure optimal patient outcomes. Rational drug prescription is a difficult task in CKD patients. These patients are at higher risk of drug related problems since they need complex therapeutic regimens that require frequent monitoring and dosage adjustments. In addition, they usually have other co-morbidities.[4]Inappropriate use of medications can increase adverse drug effects, which can be reflected by excessive length of hospital stays, excessive health care utilization and costs.[5] As CKD progresses, the drugs prescribed to these patients also increases and the prevalence of drug related problems also increases.[6] Dialysis patients require special consideration regarding prescription of drugs because of their altered pharmacokinetic and pharmacodynamics profiles.

Drug utilization studies were conducted frequently all over the world; however, in India, there is no clear picture of overall medication profile in CKD patients specially in Rajasthan. The present study was conducted to find out the prescribing pattern of drugs in chronic kidney disease patients on maintenance hemodialysis which will be helpful in generating data to evaluate, monitor and if possible, suggest modifications in prescribing practices to make medical care rational in hemodialysis patients.

Materials and Methods

A cross sectional observational study wascarried out in Department of Pharmacology and Department of Nephrology, SMS Medical College, Jaipur (Rajasthan) from April 2017 to March 2018. Prior approval from institutional ethics committee was taken. After taking informed consent eligible patients undergoing hemodialysis in Nephrology Department of the institute were recruited for the study. Total 160 CKD patients were interviewed. Sociodemographic data like age, sex, residence, socioeconomic status, educational and occupational status were noted in a pre-designed and pre-tested performa. Details about final diagnosis, associated co-morbidities, drugs prescribed were recorded.

The data collected were entered in Microsoft Excel 2010 Spreadsheets and analyzed using MedCalc Statistical Software version 17.2. Results were expressed as percentages and proportions. Pearson's correlation coefficient (r) was calculated to show correlation between drug-drug interaction and drug per prescription.

Results

Out of 160 study participants, 121 (75.63%) were males and 39 (24.37%) were females. Majority of patients were in age group of 21-30 years (27.5%). Only 5% patients were in age group of 20 years and below. 21.25% of patients were in age group of 31-40 years, 24.4% of patients were in age group of 41-50 years, 14.4% were in age group of 51-60 years and 7.5% patients were in age group more than 60 years. Mean age of males was 39.5 ± 13.29 years while mean age of females was 40.41 ± 13.53years.

53 patients (33.13%) belonged to middle socio-economic class while 107 (66.88%) belonged to lower socio-economic class.25 patients (15.63%) were illiterate, 59 (36.9%) had primary level education, 34 (21.25%) had secondary level

education, 21 (13.13%) had senior secondary level education and 21 (13.13%) had graduation & above level education.

The employed status of study participants was observed and it was found that 127 (79.37%) were employed, while 33 (20.63%) were unemployed. Among the employed, 45 (28.13%) were semi-professionals, 35 (21.87%) were homemakers, 30 (18.75%) were semi-skilled workers, 9 (5.63%) were unskilled workers and 8 (5%) were skilled workers.

Most common associated comorbidity was anemia (98.13%) followed by hypertension (95.63), infections (22.5%), diabetes mellitus (6.85%), hypothyroidism (2.5%) and others (3.75%) (Table-1). It was observed in present study that about 6 (3.76%) prescriptions contained up to 5 drugs, 139 (86.87%) prescription contained 6-9 drugs and 15 (9.37%) prescriptions contained 10-13 drugs. Total 1255 drugs were prescribed for 160 patents (Table-2).

31 (19.38%) prescriptions contained 0-2 drug-drug interactions (DDIs), 121(75.62%) prescriptions contained 3-5 DDIs and only 1 (0.63%) prescription contained > 5 DDIs (Figure-1).Most common drugs prescribed were vitamins and minerals 402 (32.03%) followed by cardiovascular (CVS) drugs264 (21.03%), hematopoetic drugs 183 (14.58%), gastrointestinal (GI) drugs 178 (14.18) and blood alkalizers 115 (9.16%) (Table-3).

The relation between drug-drug interaction and drug per prescription is expressed in the following regression equation:

$$DDI = 0.2147x + 1.4848$$

There was a strong correlation between drug-drug interaction and drug per prescription (p<0.001, r:0.2606) (Table-4 &Figure-2).

Majority of patients were highly adherent to therapy 130 (81.25%) while 30 (18.75%) of patients showed medium adherence to therapy (Figure-3).

Table-1: Distribution of study subjects according to associated comorbidities

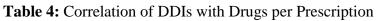| Associated Comorbidities	Number[*] (n)	Percentage (%)
Anemia	157	98.13
Hypertension	153	95.63
Infections	36	22.50
Diabetes Mellitus	11	6.88
Hypothyroidism	4	2.50
Other	6	3.75

[*]Multiple responses

Table-2: Distribution of study subjects according to drugs per prescription

Drugs Per Prescription	CKD Patients		Drugs Prescribed	
	(n)	(%)	(n)	(%)
4	1	0.63	4	0.32
5	5	3.13	25	1.99
6	16	10	96	7.65
7	43	26.87	301	23.98
8	50	31.25	400	31.87
9	30	18.75	270	21.51
10	11	6.87	110	8.76
11	1	0.63	11	0.88
12	1	0.63	12	0.96
13	2	1.25	26	2.07
Total	**160**	**100.00**	**1255**	**100.00**

Table-3: Distribution of Various Group of Drugs Prescribed

Drugs	Number	Percentage
Cardiovascular Drugs	264	21.03
Gastrointestinal Drugs	178	14.18
Anti Diabetic Drugs	7	0.56
Hematopoietic Drugs	183	14.58
Phosphate Binders	22	1.75
Vitamin and Minerals	402	32.03
Antibiotics	59	4.70
Blood Alkalizer	115	9.16
Other	25	1.99
Total	**1255**	**100.00**

Table 4: Correlation of DDIs with Drugs per Prescription

Drugs/ Prescription	Drug-Drug Interaction														
	0		1		2		3		4		5		6		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
4	0	0.00	1	0.63	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	**1**	**0.63**
5	1	0.63	2	1.25	1	0.63	1	0.63	0	0.00	0	0.00	0	0.00	**5**	**2.50**
6	2	1.25	1	0.63	2	1.25	7	4.38	4	2.50	0	0.00	0	0.00	**16**	**10.00**
7	0	0.00	4	2.50	1	0.63	21	13.13	17	10.63	0	0.00	0	0.00	**43**	**26.88**
8	0	0.00	5	2.50	3	1.88	12	7.50	28	17.50	2	1.25	0	0.00	**50**	**31.25**
9	0	0.00	3	1.88	2	1.25	11	6.88	13	8.13	1	0.63	0	0.00	**30**	**18.75**
10	0	0.00	1	0.63	1	0.63	2	1.25	4	2.50	2	1.25	1	0.63	**11**	**6.88**
11	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.63	0	0.00	**1**	**0.63**
12	1	0.63	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	**0**	**0.00**
13	0	0.00	0	0.00	0	0.00	1	0.63	0	0.00	1	0.63	0	0.00	**2**	**1.25**
Total	**4**	**2.50**	**17**	**10.63**	**10**	**6.25**	**55**	**34.38**	**66**	**41.25**	**7**	**4.38**	**1**	**0.63**	**160**	**100**

Figure-1: Distribution of study subjects according to drug-drug interactions

$$y = 0.2147x + 1.4848$$
$$R^2 = 0.0679$$

Figure-2: Correlation of DDIs with Drugs per Prescription

Figure-3: Distribution of patient's adherence to therapy according to Morisky Medication Adherence Scale

Discussion

Chronic kidney disease (CKD) has numerous causes. The most common causes of CKD are diabetes mellitus and long-term, uncontrolled hypertension.[7] Polycystic kidney disease is another well-known cause of CKD. The majority of people afflicted with polycystic kidney disease have a family history of the disease. Other genetic illnesses affect kidney function, as well. Overuse of common drugs such as ibuprofen, and acetaminophen (paracetamol) can also cause chronic kidney disease.[8] Some infectious disease agents, such as hantavirus, can attack the kidneys, causing kidney failure.[9]
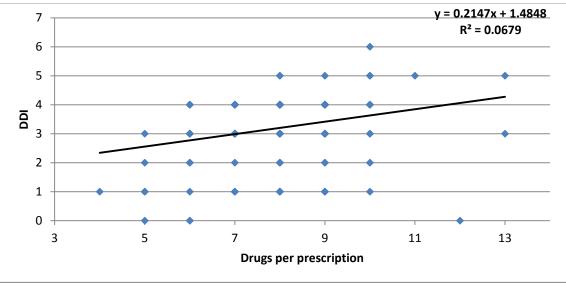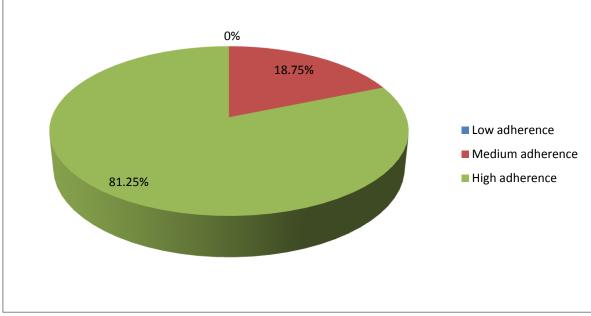
The present study showed male predominance 75.3%, and mean age to be 40 years which was similar to previous studies.[10-11] This highlighted that males were more prone to develop CKD than females because of formers association with risk factors like smoking, alcohol, hypertension (HTN) and hyperlipidemia. It was highlighted by present study that CKD was common in middle and low socio-economic classes and majority of sufferers were illiterates or primary educated, although most of them were employed. No comparable data were found in previous studies.

The mean number of drugs per prescription was 7.84 ± 1.4, suggestive of polypharmacy.

Polypharmacy is defined as use of 5 or more drugs to a patient at a time. However, in view of complex nature of the disease and coexisting morbidities of CKD, few researchers have suggested the use of more than 9 drugs at a time to be considered as polypharmacy.[12] The result of present study was similar to previous studies that found the mean number to be 7.2, 7.49 and 7.87 respectively.[13-15]

Most common drugs prescribed in this study were vitamins and minerals (32.03%) followed by cardiovascular drugs (21.03%), hematopoetic drugs (14.58%), gastrointestinal drugs (14.18%) and blood alkalizers (9.16%). These finding were similar to another study from India where most common drugs prescribed were vitamin and minerals (24.71%) followed by cardiovascular drugs (22.14%) and cematopoetic drugs (2.15%).[16] However results were differed from other studies where most common prescribed drugs were CVS drugs (42%)[10], calcium and phosphate metabolism (88%)[13] and Calcium carbonate (77.1%)[14].

In spite of high prevalence of anemia (98.13%), erythropoietin was under prescribed. In the present study erythropoietin stimulating agent (ESA) was used along with oral iron folic acid (IFA) in 34 (21.65%) of anemic patients. In rest of

anemic patients only oral IFA was used. This was lower than other studies (60%)[13] and higher than other studies where ESAs were not used and anemic patients were treated only with oral iron preparations.[10,11]

Among 11 diabetes mellitus patients only 7 (63%) received antidiabetic medications. Insulin was used in 4 (57%) and oral Teneligliptin was used in 3 (43%) diabetic patients. These findings strongly support hypothesis that requirement of antidiabetic medication falls in CKD patients. The results were similar to previous studies .[11,14]

Hypertension was the second most common comorbidity in the study (95.63%). Among the drugs to treat hypertension most commonly used were calcium channel blockers (11.55%), followed by alfa-2 agonists (4.71%), diuretics (3.35%), beta-blockers (0.96%) and alfa-blockers (0.49%). The result was contradictory to other studies where among cardiovascular drugs, diuretics[10,16] and Beta-blockers[15] were the most commonly prescribed anti hypertensives.

Hyperphosphatemia is among the most common metabolic complications of end stage renal disease. Large observational studies had identified hyperphosphatemia as an independent risk factor for cardiovascular disease and mortality on dialysis. Administration of dietary phosphorus binders to block intestinal phosphorus absorption is the cornerstone of therapy for hyperphosphatemia.[17] Of all prescribed drugs 1.99% were phosphate binders. Sevelemar (1.19%) was most frequently prescribed phosphate binder followed by calcium acetate (0.48%) and lanthanum carbonate (0.08%). Results of this study differs from other studies [13,14] where calcium carbonate was the most commonly prescribed phosphate binder. The reason behind under use of Sevelemar and other calcium free phosphate binders in present study and in previous studies was their higher cost.

Antibiotics are required in hemodialysis patients for reasons such as infection arising from vascular access, urinary or respiratory tract infections and sepsis. Total antibiotics prescribed in present study were 5.33% which were used in patients having different kind of infective conditions (22.5%). These antibiotics were used only when clear indication of infection was present, showing judicious use of antibiotics by the treating physicians. Most commonly used group of antibiotics was fluoroquinolones (1.82%), followed by cephalosporins (1.28%). Antibiotics must be used when there is presence of infection or prophylactically to prevent the infections. One of the previous studies[18] showed irrational use of antibiotics as (82%) of patients were prescribed antibiotics with no clear indication for prescribing them.

The number of prescriptions with potential drug-drug interactions (DDIs) in this study was high (97.5%). This was higher than other studies (89.1%)[14], (76.09%)[15], (95.9%)[16], (82.1%) [18]. The number DDIs increased with increase in number of drugs per prescription. The mean number of DDIs per prescription in our study were 3.17 ± 1.16. This was lower than previous study 15.69 ± 11[16] and higher than other studies (2.7)[15], (2)[18]. Some of the potentially interacting combinations noted in our study were, Iron folic acid + Calcium, Iron folic acid + Proton pump inhibitors, Sodium bicarbonate + Iron folic acid, Nifedipine + Calcium.

Adherence is a major concern in the therapy of CKD. World Health Organization estimates that only half of people with chronic diseases take their medications consistently as prescribed. Non-adherence to medication can be harmful as well as expensive for patients. In the present study adherence level was high in 130 (81.25%) patients and medium in 30 (18.75%) patients. Number of patients with high adherence in this study was lower than previous study (93.6%)[19], and higher than previous studies (7.3%)[20], (28.09%)[21], (66.2%)[22] while number of patients with medium adherence in present study was lower than previous studies (55.3%)[20], (40.45%)[21].Patients with low adherence were not recorded in the study, whereas in previous studies low adherence was found to be higher (6.4%)[19], (37.3%)[20]

and(33.8%)[22]. The probable reason for high adherence to therapy in our study was positive physician-patients relationship, and availability of required medicines for free from the hospital.

Conclusion

The present study is limited by its sample size, unicentric nature and hospital-based evaluation. However, it had generated a profile of drug use in Indian CKD patients on hemodialysis that can serve as the basis for future comparisons. The study may also help to identify educational and quality improvement opportunities to prevent medication-related problems in this population. It had identified certain areas of concern such as polypharmacy, underuse of ESAs and calcium free phosphate binders, high incidence of potential DDIs and under evaluation and treatment of mental health conditions in hemodialysis patients.

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