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Assessment of Prescription Pattern of Diuretics in Patients with Cardiovascular and Kidney Disease

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ABSTRACT

BACKGROUND: A diuretic is defined as any substance that increases urine flow and thereby water excretion. Diuretics are among the most commonly recommended drugs for the treatment of cardiovascular disease and chronic kidney diseases. **OBJECTIVE:** The primary goal of the study is to analyze the prescription pattern of diuretic in cardiovascular and chronic renal diseases in a tertiary care hospital in Bangalore**. METHOD:** It was a prospective observational study, a sample size of 150 patients' prescription details was checked and the current prescription practice of clinicians (indications, regimen, duration) and identification of potential ADRs was checked and compared with various scales. Another aspect of the study is to look at the clinical effectiveness and the side effects encountered by the patients. **RESULT:** The prescription patterns were done for 150 patients who were taking diuretics for the treatment of CVD and CKD. On assessment it was found that diuretics were mostly prescribed for patients with Cardiovascular issues (53%), followed by renal diseases (24%) then for a combination of both (23%). Furosemide was the most prescribed (64 out of 150) diuretic among the other diuretics. Potential ADRs caused were also studied and compared for their risks. Electrolyte Imbalance resulting in Hyponatremia was the most recurring ADR (51%) followed by Hypokalemia (35%). These ADRs were compared and classified based on the Naranjo scale (Doubtful-54%, Possible-25%, and Probable-20%).**CONCLUSION:**In the assessment of current prescribing patterns of diuretics, our study raises awareness of the potential ADRs, Identifying and monitoring drug interactions has a significant part in forming a standard therapeutic plan will reduce the occurrence of adverse events and their severity in hospitalized patients and suggests prescribers about alternatives to reduce the adverse events.

KEYWORDS: Diuretics, CVD,CKD, ADR

ABBREVIATION:CVD -Cardiovascular disease, CKD - Chronic Kidney Disease, ADR - Adverse Drug Reaction

I. INTRODUCTION

A diuretic is defined as any substance that increases urine flow and thereby water excretion. Diuretics are among the most commonly recommended drugs in patients with Cardiovascular and Renal diseases, and the majority act by reducing sodium chloride reabsorption at different sites in the nephron, thereby increasing urinary sodium and, consequently, water loss.[1] To understand more about the clinical applications of diuretics, it is necessary to know the pharmacology of the various classes of diuretics. Various classes of diuretics have different mechanisms of action, but various forms of diuretics from one class have similar pharmacological characteristics. For instance, since all loopdiuretics operate similarly, the addition of another loop diuretic after one with an appropriate dosage fails to show response is not warranted. Instead, combination therapy with the administration of different classes of diuretics is recommended. Thiazide diuretics work by blocking the sodium-chloride transporter, and loop diuretics act by inhibiting the sodium-potassium-chloride pump in the thick ascending limb of the loop of Henle. Amiloride and triamterene block apical sodium channels in the distal nephron. All diuretics except spironolactone reach these luminal transport sites through the tubular fluid. Spironolactone competitively binds receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. Except for osmotic diuretics, all diuretics are actively secreted into the

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urine by proximal tubule cells. Loops, thiazides, and acetazolamide are secreted through the organic-acid pathway, while amiloride and triamterene are secreted through the organic-based pathway. These drugs escape ultrafiltration at the glomerulus due to their high protein binding, more than 95%. [2]

Adverse Effects of Diuretics

Thiazide diuretics induce hypokalemia, which may lead to arrhythmia. Increased levels of serum glucose in the blood may be induced by a hypokalemic state. Glucose intolerance can be resolved by the correction of potassium levels. Thiazides compete with uric acid in renal tubular secretion, which ultimately leads to hyperuricemia. This state can be managed by administering uric acid-lowering medications like allopurinol alongside thiazides**.**

Loop diuretics are known to cause intestinal nephritis and skin reactions. Loop diuretics have to be carefully monitored, especially in high doses, as they can precipitate transient ototoxicity. Administering loop diuretics is also associated with hypokalemia, which could cause cardiac arrhythmias and lead to mortality. Loop and thiazide diuretics deplete the body not only with potassium but also with magnesium. Their synergistic use results in even more cation losses.[3]

For recovering from this deficiency, oral supplements and potassium-sparing agents are recommended. Gynecomastia is usually induced by the blocking of mineralocorticoid receptors caused by spironolactone. The major electrolyte imbalance induced by spironolactone is hyperkalemia. A combination of spironolactone and furosemide is more susceptible to inducing gastrointestinal side effects and gynecomastia than a combination of amiloride and furosemide.[4]

II. METHODOLOGY

A Prospective Observational study was conducted in the in-patient department (General medicine, Cardiology, Nephrology) of a tertiary care hospital. 150 patientsadministered withdiuretics were assessed to derive useful recommendation to the current prescription practice.All adult patients (over 18 years) were included for the study and those patients who were unwilling to get involved in the study and those who were immune-compromised were excluded from the study. The data obtained from the patient profile and medication chart in the daily ward rounds were then analyzed and documented in a self-designed structured data form.The prescribing pattern of therapy was assessed based on the patient's diagnosis with the help of demographic details age, sex, weight, height, date of admission, date of discharge, and BSI. The electrolyte imbalance induced by diuretics was examined based on the lab records of patients and then classified by the Naranjo scale and data was finally analyzed using Microsoft Excel.

III. RESULTS

DISTRIBUTION OF USE OF DIURETICS BASED ON AGE:

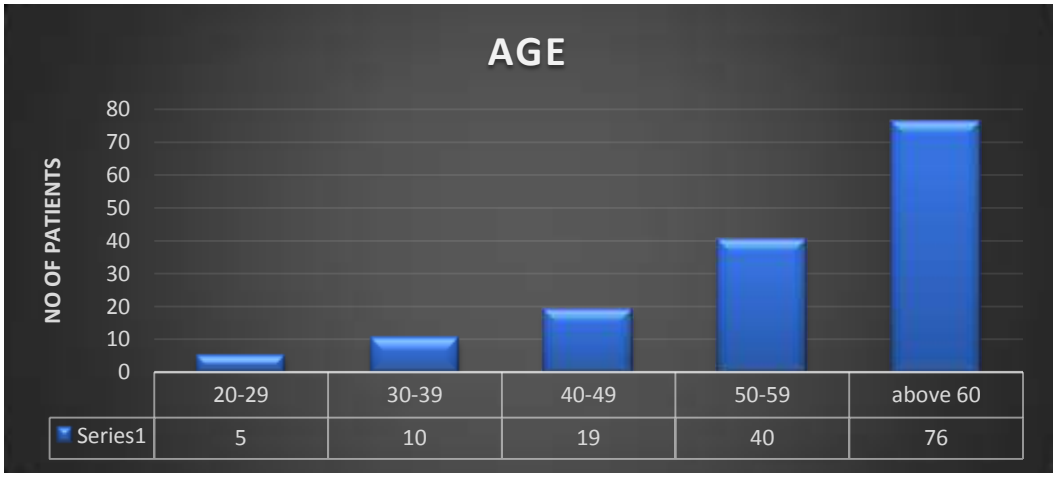

Figure1. Distribution of use of diuretics based on age

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FIGURE 1: Out of the 150 subjects, 76 patients above the age of 60 were found to be the largest. As age decreases the use of diuretics was observed to decrease. The lowest age group of 20-29 had only 5 patients.

PROPORTION OF DIURETICS BASED ON CLASSIFICATION:

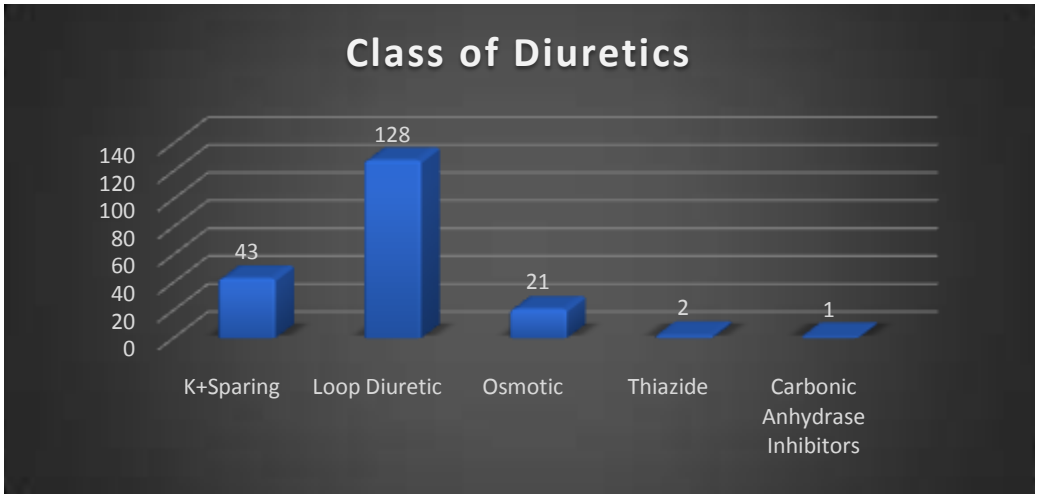

Figure 2. Proportion of Diuretics based on the classification

FIGURE 2:A total of 195 drugs were prescribed to 150 patients. Analysis showed that loop diuretics were the most commonly prescribed class.

COMPARISON OF ROUTE OF ADMINISTRATION:

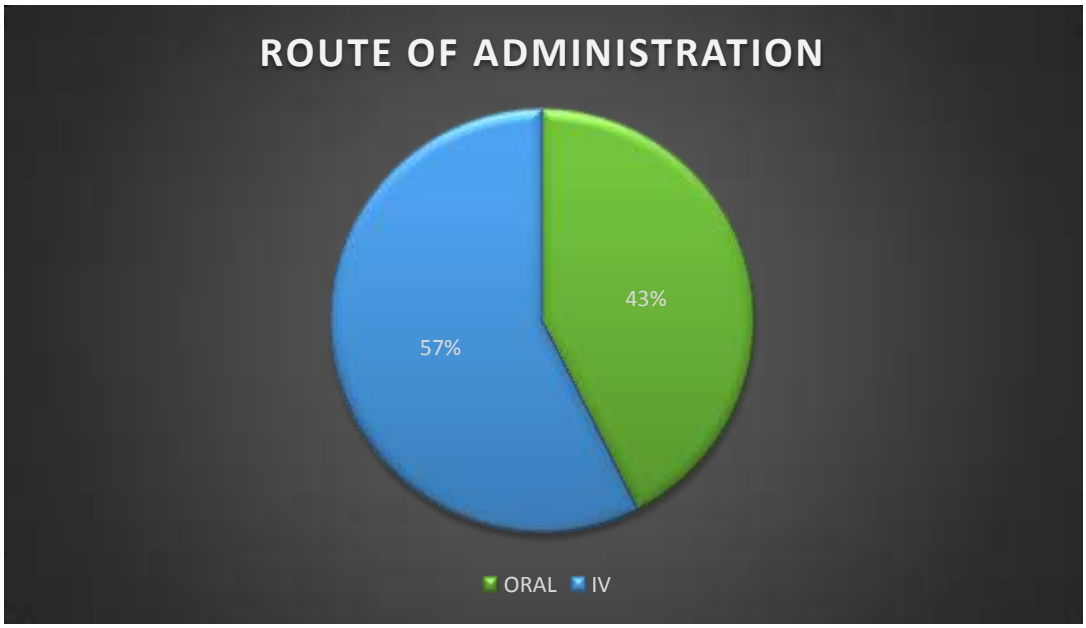

Figure 3. Comparison of Route of Administration

FIGURE 3:Based on the prescribing patterns, it was found that 57% of diuretic drugs were administered via the intravenous route while only 43% of diuretics were administered through the oral route.

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DIFFERENT INDICATIONS OF DIURETICS:

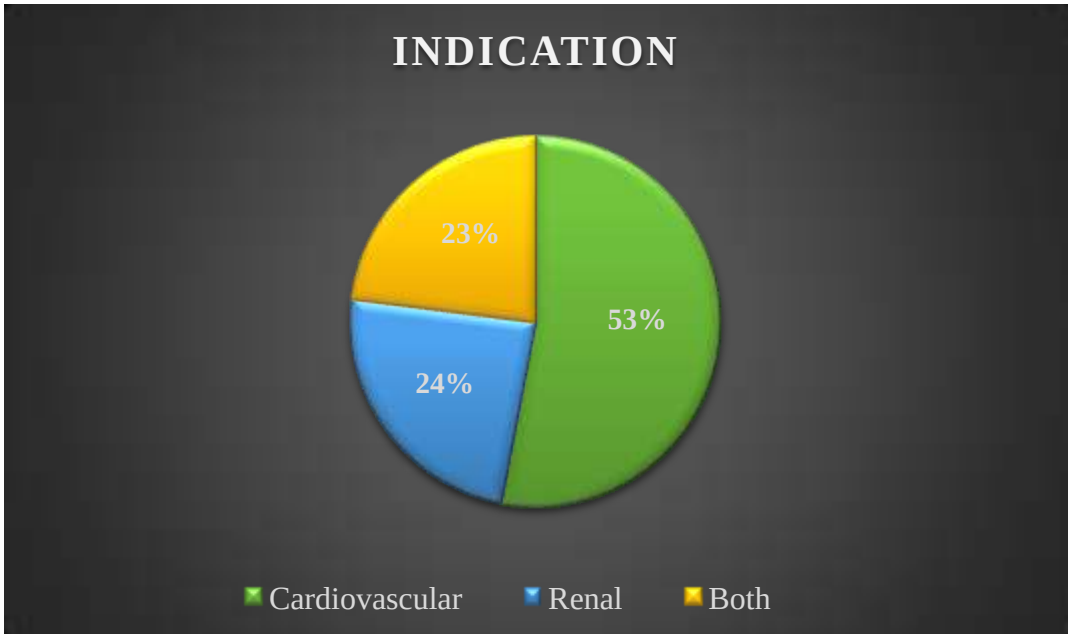

Figure 4. Different Indications of Diuretics

FIGURE 4:Diuretics are more frequently administered for cardiovascular issues (53%), followed closely by renal diseases with 24%. A combination of Cardiovascular and renal diseases also required the use of diuretics (23%).

PRESCRIPTION PATTERN OF DIURETICS BASED ON CLASSIFICATION:

Table 1: Prescription Pattern of Diuretics based on Classification

SL.NO	CLASS OF DRUG	DRUGS	DOSE	FREQ	ROA	TOTAL DRUG
1	LOOP DIURETICS	T.FUROSEMIDE	20MG 40MG 80MG	BD BD BD	PO	5 6 1 TOTAL=12
		INJ.FUROSEMIDE	20MG 40MG INF	BD BD VARIABLE	IV	50 33 8 TOTAL=91
		T.TORSEMIDE	5MG 10MG 20MG	OD OD OD	PO	2 13 10 TOTAL=25

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2	K-SPARING	T.SPIRONOLACTONE	25MG 50MG	OD OD	PO	23 20 TOTAL=43
3	OSMOTIC DIURETICS	INJ.MANNITOL	100 ML	TID/BD	IV	TOTAL=21
4	THIAZIDE DIURETICS	T.HCTZ	12.5 MG	OD	PO	TOTAL=2
5	CARBONIC ANHYDRASE INHIBITORS	T.ACETAZOLAMIDE	250MG	BD	PO	TOTAL=1
	TOTAL				**PO=83** **IV=112**	**195**

TABLE 1: A total of 195 diuretic drugs were prescribed to 150 patients. Loop diuretics (Furosemide, Torsemide) were the most prescribed class of drugs (128 times), followed by K+ sparing diuretics (Spironolactone 25/50 mg), which were prescribed 43 times. Minilactone Tablets 10 s (Spironolactone 25 mg and Furosemide 20 mg) were given as a fixed dose combination two times fortwo patients.

NARANJO'S CAUSALITY ASSESSMENT OF ADR:

S.NO	TYPE OF ADRs	NO OF ADRs(N=65)	PERCENTAGE
1	DEFINED	1	1%
2	PROBABLE	13	20%
3	POSSIBLE	16	25%
4	DOUBTFUL	35	54%
TOTAL		65	100%

Table 2: Naranjo's Causality Assessment Of ADRs

TABLE 2: Based on the causality assessment of adverse drug reactions using Naranjo's Causality Assessment Scale, 65 ADRs were identified in the study population. 35 ADRs (54%) were found to be doubtful, 16 ADRs (25%)

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were possible, 13 ADRs (20%) were probable, and only 1% of ADRs were defined.

ELECTROLYTES IMBALANCE INDUCED BY DIURETICS:

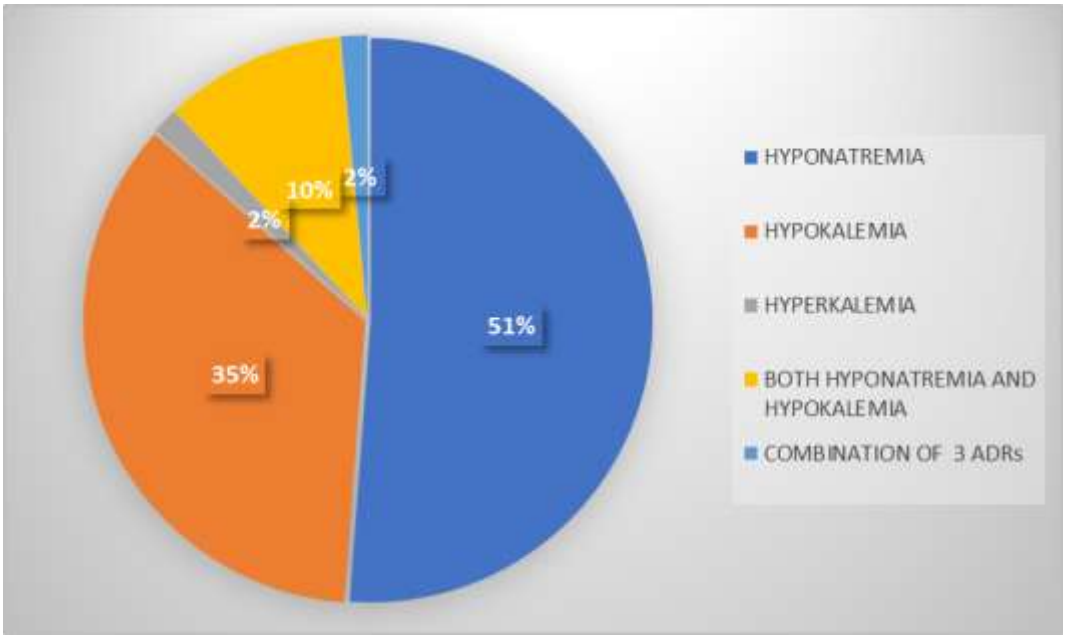

Figure 5: Electrolytes Imbalance Induced By Diuretics

FIGURE 5: In the current study, hyponatremia wasobserved in 34 patients (51%), caused by various classes of diuretics. Hypokalemia was another ADR that was found in 23 patients (35%). Both hypokalemia and hyponatremia occurred consecutively in 7 patients (10%). Hyperkalemia was observed only in one patient (2%) who had taken spironolactone. Only one patient (2%) developed a combination of three ADRs (hypokalemia, hyponatremia, and hypochloremia) due to the combination of Furosemide/Torsemide/HCTZ.

IV. DISCUSSION

DISTRIBUTION OF USE OF DIURETICS BASED ON AGE:

Geriatric patients (Above the age of 60) were the largest category (76nos. – 50.7%) using diuretics. A proportional decrease was observed in usage as the age of the patients decreased. The lowest group (20-29) had only 5 patients. As age decreases the use of diuretics was observed to decrease.

PROPORTION OF DIURETICS BASED ON CLASSIFICATION:

A total of 195 drugs were prescribed to 150 patients. These agents were categorized into different groups, where loop diuretics had the highest rate of prescription (128 drugs), followed by potassium-sparing diuretics (43), osmotic diuretics (21), thiazides (2), and carbonic anhydrase inhibitors (1), respectively.

COMPARISON OF ROUTE OF ADMINISTRATION:

Based on the prescribing patterns, it was found that 57% of diuretic drugs were administered via the intravenous route, while only 43% were administered via the oral route. The highest percentages of intravenous injections were observed for furosemide 20 mg (50 drugs), followed by injection of furosemide 40 mg (33 drugs), then by mannitol 100 ml (21 drugs), and only 8 furosemide were administered through iv-infusion with an average dose of (5mg/hr).All other types of diuretics were administered through the oral route (43%).

DIFFERENT INDICATIONS OF DIURETICS:

Diuretics are more frequently administered for cardiovascular issues (53%), followed closely by renal diseases (24%). A combination of cardiovascular and renal diseases also required the use of diuretics (23%).

PRESCRIPTION PATTERN OF DIURETICS BASED ON CLASSIFICATION:

A total of 195 diuretic drugs were prescribed to 150 patients. The loop diuretic drugs

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had the largest rate of prescription, with 128 drugs that included (furosemide (103) and torsemide (25)). 64 patients from a total of 150 patients were given either intravenous or oral furosemideas single diuretic drugs, 25 patients were given furosemide along with tabletspironolactone (25 mg or 50mg), and 2 patients underwent treatment with a fixed dose combination of Minilactone Tablet 10 s (spironolactone 25 mg + furosemide 20 mg).2 patients had taken furosemide along with mannitol, and administrationof furosemide with acetazolamide and hydrochlorothiazide in the prescriptions of 2 patients were found separately. Torsemide was another loop diuretic that was administered in 3 different doses (5mg,10mg,20mg) as a single diuretic therapy or along with other groups of diuretics.

In our study, thesecond largest groups of diuretics used were k-sparing groups of diuretics with 43 drugs (spironolactone 25 or 50 mg). The 2 drugs were administered as a fixed dose combination of Minilactone Tablet 10 s (spironolactone 25 mg + furosemide20 mg).

Injection of mannitol, an osmotic diuretic, was prescribed 21 times out of a total of 195 diuretics. Mannitol was observed as a single diuretic in the prescriptions of 18 patients, and it was also administered along with torsemide (1patient)and along with furosemide (2 patients).

Hydrochlorothiazide 12.5mg only was prescribed for one patient under fixed dose combination of tablet Telminet-H (Telmisartan 40 mg + Hctz12.5mg) and one patient took hydrochlorothiazide 12.5 mg along with other types of diuretics. Acetazolamide, a carbonic anhydrase inhibitor was prescribed for only one patient along with other types of diuretics (furosemide).

NARANJO'S CAUSALITY ASSESSMENT OF ADR:

By applying Naranjo's causality assessment scale, the 65 ADRs were categorized into 4 groups that can be followed:1- defined (1%) 2-probable (20%) 3- possible (25%), and 4- doubtful (54%).

ELECTROLYTES IMBALANCE INDUCED BY DIURETICS:

Diuretics usually promote the excretion of electrolytes which may be caused to decrease serum of electrolytes. In the current study, hyponatremia induced by various diuretics was one of the most common ADRswithan incidence rate of 51% followed by hypokalemia at 35%. Only 7 patientsdeveloped bothhypokalemia and hyponatremia simultaneously as ADRs (10%). Hyperkalemia was observed only in one patient who received spironolactone.

One patientdeveloped 3 ADRs simultaneously (hypokalemia, hyponatremia, and hypochloremia) who was on Furosemide, Torsemide, and Hydrochlorothiazide combinations, because of loop diuretics effect on (Na+/K+/2CL) co-transporter by blockingchloride-coupled sodium re-absorption in the loop of Henle lead tohypokalemia and hyponatremia and hypochloremia, where Thiazide have same action but the effect on early distal tubules. Hence the combination of these loop diuretics and Thiazideincreases sodium and chloride delivery to the collecting duct, simulating potassium secretion and causing CL- depletion. This depletion may lead to hypokalemia.

According to the study done by S. Vikas et al. (2017), hyponatremia was observed as a single ADR that was induced by various types of diuretics and then was followed by hypokalemia, and three patients had developed three adverse drug reactions simultaneously, hence not much difference was observed between these two studies.

V. CONCLUSION:

In the assessment of current prescribing patterns of diuretics, our study raises awareness of the potential ADRs, electrolyte imbalances, and their severity in hospitalized patients and suggests to prescribers about alternatives to reduce the adverse events.

Through the current study, we could assess the drug utilization pattern of diuretics for 150 patients in the cardiac care unit, HICU, ICU, and general medicine department.Among diuretics, furosemide, spironolactone, and mannitol were highly utilized in the intensive care unit and general medicine department.

The current study assessed the electrolyte imbalance induced by diuretics. Of 150 patients, 65 developed ADRs, where hyponatremia was observed in 34 patients (51%), followed by hypokalemia in 23 patients (35%). Simultaneously, both hypokalemia and hyponatremia were observed in 7 patients (10%), and only one patient had developed hyperkalemia (2%); in only one patient who received furosemide, torsemide, and hydrochlorothiazide combinations, 3 ADRs (hypokalemia, hyponatremia, and hypochloremia) were simultaneously observed (2%).

Since diuretic-induced electrolyte imbalances were observed during the current study, the clinical pharmacist can be effectively employed

to monitor the electrolyte levels to reduce the adverse effects. The pharmacist can play an important role to avoid adverse effects associated with diuretics by discussing with the prescriber about drugs and their safety, and alternatives so that an appropriate decision is made about the patient's therapeutic plan.

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