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Analysis of ADRs with Hypokalaemia for Severity, Preventability and Causality in a Tertiary Care Centre in South India

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Abstract

Hypokalemia is one of the most frequently seen electrolyte disturbances in clinical practice. Various drugs are known to induce hypokalemia, such as furosemide, thiazides, dicloxacillin, ampicillin, etc. This study aimed to assess hypokalemia adverse drug reactions (ADRs) for severity, preventability, and causality in a tertiary care centre in the southern part of India. It is a retrospective, cross-sectional study. Data collected at DMWIMS Medical College, India, as per the ongoing pharmacovigilance program of India from November 1st, 2016 to October 30th, 2017 (12 months period) was included for analysis in this study. The SADR form published by the Government of India under the PVPI program was used for collecting the data. In-patients who were on at least one medication and experienced hypokalemia ADRs with or without other symptoms or signs were included. Both primary suspected drugs and concomitantly prescribed drugs were analyzed. For the assessment of ADRs, modified Hartwig and Siegel assessment scales and plasma K^+ level criteria were used for severity, Schumock and Thornton criteria for preventability, the WHO-UMC scale, and Naranjo's algorithm for causality, respectively. Sixty hypokalemia ADRs were considered for analysis. Both genders were equally affected, with a mean age of 64.28 ± 3.02 years. Four groups of drugs were suspected to cause hypokalemia viz., anti-asthmatics (36.67%), diuretics (31.67%), antibiotics (18.33%), and antidiabetics (13.33 polypharmacy was reported in 43.33% of cases, with 4.40 ± 01.689 drugs prescribed on average. To summarize, hypokalemia is a preventable ADR and minor variations in serum K^+ levels can have a negative impact on patients' outcomes and mortality. FDC of Levosalbutamol with Ipratropium Bromide was the most common causative agent suspected of causing hypokalemia. Elderly patients receiving one or more drugs that are known to alter K+ levels, need close monitoring, and correction of hypokalemia should be done to improve prognosis. Further studies are required to understand the mechanisms involved in DDIs and DDiIs to derive preventive strategies.

Keywords: : Hypokalemia, Adverse Drug Reactions, Causality, Severity, Preventability, Pharmacovigilance

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Introduction

The physiological functions of many human cells, such as nerve cells, and skeletal and cardiac muscles, require homeostasis of intra- and extracellular potassium. About 98% of cation potassium (K^+) remain inside the cell (intracellular fluid (ICF)) and the remaining 2% is found in extracellular space (ECF). Normal plasma K^+ levels range from 3.5 to 5 mmol/L. Alteration in serum K^+ levels can have lethal consequences.[1-3]

Serum K^+ levels may be altered due to dietary deficiencies, underlying diseases that induce acid-base disturbances, changed tonicity of body fluids, excretion through sweat, the gastrointestinal tract, and the renal route. It is also altered by hormones such as aldosterone, insulin, catecholamines, etc. Coexisting hypomagnesemia promotes potassium wasting as it reduces the function of Sodium-Potassium Adenosine Tri-Phosphatase (Na^+-K^+ ATPase) pump.[1]

Various drugs are known to induce hypokalemia, such as furosemide, thiazides, dicloxacillin, ampicillin, amphotericin B, aminoglycosides, penicillin, salbutamol, formoterol, isoproterenol, pseudoephedrine, terbutaline, salmeterol, hydrocortisone, fludrocortisone, prednisone, insulin, and adrenocorticotrophic hormone (ACTH), etc.[1,3]

Hypokalemia is a frequently seen electrolyte disturbance in clinical practice. A serum K^+ level below 3.5 mmol/L is considered as hypokalemia. It can be graded as mild (> 3.0–3.5 mmol/L), moderate (2.5–3.0 mmol/L), and severe (< 2.5 mmol/L) hypokalemia. The severity of clinical signs and symptoms can vary from asymptomatic in mild cases to cramping, malaise, myalgia, and weakness in moderate hypokalemia. Severe cases may present with arrhythmias, paralysis, and electrocardiogram (ECG) changes like ST-segment depression, U-wave elevation, and T-wave inversion.[1-3]

Hypokalemia in elderly patients who are suffering from cardiovascular, hepatic, or renal diseases is bound to have higher mortality and morbidity. The severity of hypokalemia had a linear relationship with the development of ventricular arrhythmia in patients with myocardial infarction. Potassium levels below 4 mmol/L are an independent predictor of mortality in heart failure patients. Choline acetylase activity is reduced in hypokalemia, leading to a depletion of acetylcholine levels. These patients may experience decreased intestinal motility and even paralytic ileus due to reduced neuromuscular function. Hypokalemia may enhance ammonia genesis and worsen the symptoms of hepatic encephalopathy, which may precipitate hepatic coma.[1]

Epidemiology studies suggest that, irrespective of gender, up to 20% of hospitalized patients may have mild, 4-5% moderate (clinically significant), and 1% severe hypokalemia. Up to 50% trauma patients and 2.5% of elderly subjects aged ≥75 years are reported to have hypokalemia.[1,4,5,6] Approximately 80% of patients on diuretics and 0.9% of those receiving antimicrobial agents reported having hypokalemia. Drug disease interactions (DDIIs) and drug-drug interactions (DDIs) are expected to enhance the possibility of hypokalemia.[1,4,5]

Although a sufficient number of publications are available on hypokalemia worldwide, there are few studies in the Indian population. Rehan HS et al., and Mayee KR et al., published on drug-induced hypokalemia in hospitalised patients, and Kunder SK et al., reported with case series analysis.[3,6,7] Therefore, investigators of this study conducted this systematic analysis of drug-induced hypokalemia in inpatients

with the objective to "assess their severity, preventability, and causality in a tertiary care centre in the southern part of India."

Methods

Institutional ethics committee approval (Ref No. IEC/DMWIMS/July/2018-007) was obtained before the initiation of this study. It was a retrospective, cross-sectional study. The study lasted for 12 months, beginning on November 1st, 2016 and ending on October 30th, 2017. Data collected as per the ongoing Pharmacovigilance Program of India (PvPI) program was used for the study, and access was limited to investigators, and confidentiality of patient identifiers was maintained.

Doctors, nurses, and pharmacists (HCPs) were encouraged to report adverse drug reactions (ADRs) through awareness programmes organized regularly in the institute. All ADRs from inpatients (wards and ICUs) were collected using the Suspected ADRs Reporting (SADR) Form of PvPI8. The completed SADR forms were collected and analyzed by a team of pharmacologists and clinical pharmacists.

Inclusion Criteria

In-patients of both genders, irrespective of age, receiving at least one medication and having hypokalemia alone or any other concomitant sign or symptom as an ADR.

Exclusion Criteria

ADRs in patients treated on an outpatient basis. ADRs due to drug abuse; accidental poisoning; intentional self-harm; blood transfusion, or its products. Incomplete forms that do not have minimum requirements such as an identifiable patient, event, reporter, and drug were excluded from analysis.

Completed SADR forms were subjected to analysis under the following parameters: age, gender, weight, single/multiple events, presence/absence of polypharmacy, DDI, the severity of the ADRs based on plasma K+ levels1 and Modified Hartwig and Siegel's Severity Assessment Scale,[9] causality based on WHO-UMC causality categories,[10] Naranjo's algorithmic scale,[11] and preventability based on the Modified Schumock and Thornton Scale.[12] In addition, analysis was done on the primary suspected drug(s), concomitant medication(s), and their therapeutic area.

Statistical Analysis

The values were expressed in frequency, proportions, mean, and standard deviation (SD), as appropriate. The unpaired student t' test was used to compare age and body weight between male and female patients. It was also used to compare K+ values in patients with or without DDI. One-way Analysis of Variance (ANOVA) was used to compare K+ values between different therapeutic groups of primary suspected drugs. $p \leq 0.05$ was considered significant. GraphPad InStat 3 statistical software was used for statistical analysis. MS Word and MS Excel were used to generate tables as necessary.

Results and Discussion

During the study period, 60 hypokalemia ADRs were reported. All the hypokalemia reports were included for analysis in the study. This ADR was found in an equal number of males (n = 30) with a mean (±SD) age of 63.50 (±11.64) years and females (n = 30) with a mean (SD) age of 65.06 (±14.42) years. Twenty-one (21) patients were aged less than 60 years. The remaining 39 patients were all over the age of 60. The median age was 64 years; the minimum was 38 years, and the maximum was 88 years. The mean (±SD) body weight of male patients was 62.33 (±07.66) kg, and for female patients, it was 54.23 (±06.87) kg. (Table 1.)

Table 1. Details of Demographic Profile, Poly-Pharmacy, Associated Events of Patients with Hypokalemia

Sl No	Parameter	Sub parameter	n	Mean	SD	p value	Comment
1	Gender	Male	30	-	-	-	No comments
		Female	30	-	-		
2	Age	Male	30	63.50	11.64	0.6451	Statistical test used is "unpaired t test".
		Female	30	65.06	14.42		
3	Weight	Male	30	62.33	07.66	0.0001	
		Female	30	54.23	06.87		
4	Single event or Multiple events	Single event (Hypokalemia Only)	47	-	-	-	Concomitant ADRs (number of patients): Bleeding (1), Blurring of Vision (1), Constipation (2), Hyperglycemia (1), Hypoglycemia (2), Hypomagnesemia (1), Hyponatremia (2), Oral candidiasis (1), Rash (1), Hypotension (1) *, Thrombocytopenia (1) * * Same patient had 3 events at a time including hypokalemia
		Multiple Events (Hypokalemia + other symptoms/signs)	13				
5	Poly-pharmacy**	No	34	04.40	01.689	-	**Definition[13,16]: Using five or more medications in the same patient at a time
		Yes	26				
6	Drug-drug interaction***	Yes	37	2.8702	0.3447	0.5784	Serum K^+ levels compared using Statistical test "unpaired t test".
		No	23	2.9200	0.2687		***. Three patients' records did not have potassium values. 57 patient's data considered for mean/SD calculation.

Table 2. Primary Suspected Drugs that Caused Hypokalemia and Their Therapeutic Area

Sl No	Therapeutic Area of Drugs (Total %)	¥Plasma K^+ Levels Mean ± SD (n)	Names of Drugs	No of Patients (%) n = 60
1	Antibiotics (18.33 %)	2.74±0.43 (10) *¥	Piperacillin + Tazobactam,	09 (15.00%)
			Cefoperazone	01 (01.67%)
			Cefoperazone + Sulbactam	01 (01.67%)
2	Anti-diabetic (13.33 %)	2.91±0.15 (7) * ¥	Insulin	08 (13.33 %)
3	Diuretic (31.67 %)	2.90±0.34 (18) * ¥	Furosemide	13 (21.67 %)
			Hydrochlorothiazide	03 (05.00 %)
			Furosemide + Spironolactone	01 (01.67%)
			Spironolactone + Torsemide	01 (01.67%)
			Torsemide	01 (01.67%)
4	Anti-Asthmatics (36.67 %)	2.94±0.28 (22) ¥	Levosalbutamol + Ipratropium Bromide	16 (26.67 %)
			Salbutamol	04 (06.67 %)
			Levosalbutamol	02 (03.33%)

*one patient in each group did not had K^+ values, they were excluded from analysis.

¥Intergroup comparison of K^+ values with One-way Analysis of Variance (ANOVA) done and P=0.4431 (no significant difference noted).

Hypokalemia is common in community dwellers (2.5%) aged 55 years and older, in-patients (20%), and those admitted to the emergency department (39%). According to Liamis G et al., women may have twice the risk of hypokalemia as male patients.[5,14] Reports suggest that pediatric inpatients suffering from fever and needing critical care are expected to suffer from hypokalemia. A severe form of it may be seen in patients with diarrhea and severe malnutrition.[15] In our study, 65% (39/60) of the patients were in the over-60 age group. However, an equal number of male and female patients suffered from hypokalemia. Therefore, treating physicians should expect such electrolyte imbalances irrespective of age and gender while treating these patients.

Details of drugs that are suspected to cause hypokalemia are shown in Table 2. They are grouped under four therapeutic areas, namely: anti-asthmatics (36.67 %), diuretics (31.67 %), antibiotics (18.33 %), and anti-diabetics (13.33 %). Among anti-asthmatics, FDC of Levosalbutamol (β2 agonist) with Ipratropium Bromide (26.67 %) was the most frequently suspected cause of hypokalemia.

Table 3. Concomitant Medications and Their Frequency of Use in Patients with Hypokalemia ADRs

Sl No	Concomitant medication system	No of Patients n=60 (%)	Names of Drugs (frequency of use)
1	Drugs Affecting Gastrointestinal System	38 (63.33 %)	Pantoprazole (35), Ranitidine (3), Omeprazole (2), Ondansetron (2)
2	Antibiotics	26 (43.33%)	Piperacillin (8), Tazobactam (8), Amoxicillin (8), Clavulanic acid (7), Metronidazole (5), Sulbactam (5), Cefoperazone (4), Ceftriaxone (3), Azithromycin (2), Meropenem (2), Cefixime (1), Ciprofloxacin (1), Clotrimazole (1), Doxycycline (1), Nitrofurantoin (1), Oseltamivir (1)
3	Cardiovascular Drugs	17 (28.33 %)	Amlodipine (4), Aspirin (1), Bisoprolol (1), Digoxin (2), Hydralazine (1), Isosorbide Dinitrate (1), Ivabradine (2), Losartan (1), Metolazone (1), Moxonidine (1), Telmisartan (1), Verapamil (1)
4	Drugs Affecting Immune System	09 (15.00 %)	Hydrocortisone (6), Methyl Prednisolone (2), Dexamethasone (1)
5	Anti-Inflammatory, Analgesic, Anti-gout	07 (11.67 %)	Paracetamol (3), Aspirin (1), Diclofenac (1), Febuxostat (1), Tramadol (1), Allopurinol (1)
6	Drugs Affecting Respiratory System	07 (11.67 %)	Deriphyllin (5), Levosalbutamol (2), Budesonide (1), Ipratropium Bromide (1),
7	Anti-diabetics	06 (10.00 %)	Insulin (4), Metformin (2), Glimepiride (2), Insulin Aspart (1), Insulin Glargine (1)
8	Anti-coagulants	06 (10.00 %)	Clopidogrel (4), Aspirin (1), Enoxaparin (1), Acenocoumarol (1), Cilostazol (1)
9	Drugs Affecting Genital and Urinary tract	04 (06.67 %)	Prazosin (1), Sildenafil (1), Tamsulosin (1), Stanozolol (1)
10	Lipid Lowering Drugs	04 (06.67 %)	Atorvastatin (4)
11	Drugs Affecting Electrolyte Levels	04 (06.67 %)	Furosemide (2), Calcium Polystyrene Sulphonate, Potassium Chloride (1), Sodium Bicarbonate (1)
12	Thyroid Hormone	01 (1.67 %)	Levothyroxine (1)

Furosemide (21.67%), FDC of Piperacillin with Tazobactum (15.00%), and Insulin (13.33%) were the common drugs suspected from other therapeutic areas. As per Hsu E et al. and Veltri KT et al., beta-2 agonists and xanthines are known to produce hypokalemia due to an inward shift of potassium into the cells due to an effect on the membrane-bound Na+/K+-ATPase1,[17]. In contrast, corticosteroids increase renal potassium loss.[1] Furosemide and thiazides are kaliuretic diuretics and can worsen coexisting hypokalemia.[18]

Hypokalemia may be worsened in diabetic patients due to trans-cellular shifts after using high dosages of insulin.[19] Beta-lactam antibiotics are reported to produce hypokalemia through two mechanisms; first, they increase the transepithelial electronegativity by acting as nonabsorbable anions in the distal nephron. This leads to increased distal sodium delivery and potassium excretion; second, they are administered with large amounts of sodium, which can result in solute diuresis. This kind of solute diuresis can cause potassium excretion through the BK channels due to a high flow rate in the cortical collecting duct.[20,21]

According to the literature search, all 60 (100%) ADRs in this study were suspected to be caused by drugs that were already known to cause hypokalemia1.[3,7] Therefore, the majority of the ADRs could have been prevented if therapeutic drug monitoring (TDM) protocols had been implemented. Drugs used for treating GIT diseases (63.33%), infections (43.33%), CVS diseases (28.33%), and inflammation and immune diseases (15.00%) were the common concomitant medications prescribed, respectively, in descending order (Table 3).

Fifty-nine (98.33%) patients received more than one drug, and on an average patients received 4.40±01.689 drugs per patient. Polypharmacy was identified in 43.33% (26/60) of the cases. Further systematic studies are required to understand the mechanisms involved in the development of hypokalemia through DDI when more than one drug known to cause hypokalemia is used together

Two methods were applied for severity analysis (able No. 4). Both methods gave approximately similar results. Based on plasma K^+ levels[1] and the Modified Hartwig and Siegel's Severity Assessment Scale,[9] mild to moderate cases totaled 50 (83.33%) and 49 (81.66%) events, respectively. Forty-seven (78.33%) patients had a single event, i.e., non-symptomatic hypokalemia, and the remaining 13 patients (21.66%) had more than one sign or symptom. As per literature, patients with mild to moderate hypokalemia may not show any symptoms or may have some vague symptoms of systemic diseases like heart failure, ADRs of anti-asthmatics, or other electrolyte disturbances, e.g. sodium retention.[7]

Diuretics, such as hydrochlorothiazide, frequently cause mild hypokalemia at the start of treatment, which may resolve spontaneously depending on the underlying disease and severity.[1,5] According to Nasralla HA et al. and Lemieux G et al., 12% of hypokalemia patients may experience symptoms such as generalized weakness, muscle weakness, fatigue, and cramps, particularly those taking diuretics and steroids1.[5,7] ECG monitoring may detect changes like prominent U waves, flat T waves, and ST segment depression in hypokalemia. Digitalis intake in hypokalemia patients may induce palpitations and ventricular and supraventricular tachyarrhythmias. Monitoring the ECG will thus be beneficial in these patients.[14]

In our study, the majority of ADRs were considered to be possibly related to the primary suspected drugs. As per the WHO-UMC scale,

Table 4. Assessment of Severity of Hypokalemia

Sl No	Parameter		Based on plasma K^+ concentration*		Modified Hartwig and Siegel's Severity Assessment Scale
			No of Patients (%)	Mean (SD) In mmol/L	No of Patients (%)
1	ADR Severity$	Mild	30 (50.00%)	3.103 (0.1189)	02 (03.33%)
		Moderate	20 (33.33%)	2.795 (0.1791)	47 (78.33%)
		Severe	07 (11.66%)	2.228 (0.0951)	11 (18.33%)
2	Average of K^+ conc.	Lower Level Reported***	57**	2.887 (0.3185)	-
		Higher Level Reported ***	57**	3.768 (0.7209)	-

Note:

*Severity based on lowest recorded K^+ value in mmol/L: **a).** Mild = less than 3.6 and more than/ 3.0;

b). Moderate 2.5 to 3.0;

c). Severe less than 2.5.

**Three patients records did not have potassium values. 57 patient's data considered for mean/SD calculation.

***If only one value available, then same value was considered for both lower and higher level for calculation purposes.

$ According to definition of Serious Adverse Event (SAE)[22] 47 where SAEs were considered as SAEs, and remaining 13 were not.

The reasons for considering SAE: **a).** Hospitalization was prolonged in 43 cases;

b). Four patients had life threatening events.

43 (71.66%) events and, according to the Naranjo ADR probability scale, 40 (66.66%) events were considered possibly related. All 60 ADRs were considered to be definitely preventable. (Table 5). These results were considered to be similar to those reported in Mayee et al., study.[7]

Serum K^+ monitoring is part of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score or the Simplified Acute Physiology Score (SAPS). Both hypokalemia and hyperkalemia will cause the scores to rise. This indicates that patients admitted to the intensive care unit with abnormal potassium levels have a worse prognosis.[4] Abensur VL et al, reported that serum potassium disturbances are bound to increase mortality in patients with chronic diseases like diabetes mellitus, hypertension, ischemic heart diseases, congestive heart failure, and kidney failure. Both hyper- and hypokalemia are expected to worsen these patients' prognoses.[23]

Renal or non-renal loss of K^+ may lead to hypokalemia due to drug use of drug(s) or disturbance in homeostasis. Renal loss of K^+ occurs due to acidosis in the renal tubules,

hormonal disturbances regulating electrolytes, hypomagnesemia, starvation, dementia, and anorexia. Homeostasis may be disturbed due to a transient intracellular K^+ shift in metabolic alkalosis and inadequate dietary intake. Non-renal loss may occur in diarrhea, vomiting, excessive perspiration, and dehydration with subsequent secondary hyperaldosteronism. Procedures such as nasogastric suctioning, laxative use, hemo, and peritoneal dialysis can all cause hypokalemia.[14]

As discussed earlier, the majority of ADRs could have been prevented if therapeutic drug monitoring (TDM) protocols were implemented. This was again supported when preventability was assessed by applying the Modified Schumock and Thornton scale. Preventive strategies may include the use of a low-salt diet, but rich in potassium, magnesium, and chloride (either through foods enriched with these elements or through potassium chloride supplements); management of the underlying disease or elimination of the causative factor; discontinuation of laxatives; use of lower doses of drugs known to cause hypokalemia; and/or use of potassium-sparing drugs.[1,5] Joon-myoung K et al. used 6- and 12-lead ECGs to detect and monitor electrolyte imbalances in serum potassium, sodium, and calcium by integrating artificial intelligence (AI) and computer-triggered reminders (CTR).

Similarly, AI and CTR tools can be used to prevent hypokalemia induced by DDIs and DDIIs.[24-26] Integration of hospital information management systems to include clinical pharmacologists in the internal referral systems may help the hospitals to utilize their services related to TDM, causality assessment, prescription auditing, and DDI/DDIIs predictions to prevent severe forms of ADRs.

Advantages and Limitations of the Study

This is the first study published on this subject from Kerala, south India. Therefore, this study adds important value to the existing knowledge on hypokalemia. As mentioned in the methodology section, ADRs experienced by outpatients, those due to OTC medication intake, and domestic medication consumption were excluded from the analysis. Our study is a retrospective cross-sectional study based on the available 12-month data. All the available cases formed the basis for analysis. An exact sample size was not calculated for this study. Therefore, we accept this as a limitation of this study.

Conclusion

Hypokalemia is a preventable ADR, and minor variations in serum K^+ levels can adversely affect the patient's outcome and may also increase mortality. In our study, four groups of drugs, such as β2 agonists, diuretics, antibiotics, and anti-diabetics, were suspected as the causative agents of hypokalemia. Any patient receiving drugs originating from one of these groups needs monitoring of serum K^+ levels, especially in those patients who are suffering from diseases known to have altered electrolyte levels. In such cases, close monitoring should be implemented, and suitable management and prevention strategies should be considered. Further studies are required to understand the mechanisms involved in DDIs and DDIIs and derive better preventive strategies.

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Table 5. Assessment of Causality and Preventability of Hypokalemia

Sl No	Causality Assessment				Preventability Assessment	
	WHO-UMC scale	n=60	Naranjo ADR probability scale	n=60	Preventable (and its reasons) or Not preventable (based on Schumock and Thornton preventability assessment scale)	n=60
1	Certain	03	Definite	0	**1.** Definitely preventable	60
2	Probable	14	Probable	20	**a.** Was there a known treatment for the Adverse Drug Reaction? *	60
3	Possible	43	Possible	40	**b.** Was required Therapeutic drug monitoring or other necessary laboratory tests not performed? *	49
4	Unlikely	00	doubtful	00	**c.** Were preventative measures not prescribed or administered to the patient? *	18
5	Conditional / Unclassified	00	-	-	**2.** Not preventable	00
6	Unassessable / Unclassifiable	0	-	-	*More than one reason attributed for preventable events	

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Conflict of Interest
None declared

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