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Delayed expression of electrolyte imbalance resulting from long term use of diuretics

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Abstract
Patients suffering from renal edema, hepatic edema, hypertension and ischaemic heart diseases receiving diuretics, were enrolled to study the type of serum electrolyte imbalance and the time lag between diuretics administration and the appearance of adverse effects. The adverse effects (6.8%) were hypokalaemia (2.9%), followed by hyponatraemia (2.4%) and hyperkalaemia (1.5%). The earliest adverse effects found at 2 month interval were hyponatraemia (22%), hypokalaemia (13%), and hyperkalaemia (3.2%). At 4-10 months interval similar ADE were detected with variable pattern. Delayed effects namely hypokalaemia (furosemide-6.4%), hyperkalaemia (spiranolactone-3.2%) were evident at as late as 12 months interval. None of the angina pectoris group showed adverse effects. Maximum patients belong to higher age 61-75 yrs; (37.5%) and most were patients of renal edema (38.7%).

Keywords: Diuretics, electrolyte imbalance, time interval, dose dependent dynamics, prognostic dilemma

Introduction
Long term administration of diuretics is known to cause adverse drug effects (ADE) such as hyperkalaemia (potassium sparing group), hypokalaemia; hyponatraemia (loop diuretic) and other[1]. Serum sodium and potassium abnormalities are deleterious for cardiac and other functions, hence their detection at proper interval (time interval between drug administration and desired effects) [1] (lag) is of utmost importance. However there are no reports regarding lag for such ADE to be evident; also no knowledge about the complex inter-relationship between the dose of diuretic, type of ADE, diagnosis and age susceptibility. You could add these,
Recommends monitoring laboratory results to minimize serious events before they occur. Laboratory monitoring for electrolyte imbalances and increased creatinine (associated with acute kidney injury) should be performed periodically.
However, after 24 months of therapy, a significant difference, which correlated with serum K^+ concentrations, emerged in the PVC rate (20% [diuretic treated] vs. 9% [placebo]).[19] Medical Research Counci. Working Party on Mild to Moderate Hypertension: Ventricular extrasystoles during thiazide treatment: substudy of MRC mild hypertension trial. *BMJ*. 1983; 287: 1249–1253. Petri M, Cumber P, Grimes L, *et al.* The metabolic effects of thiazide therapy in the elderly: a population study. *Age Ageing*. 1986; 15:151-155.

Methods
Adult male patients (25-75 yrs) attending Medicine OPD,(do the patients attend opd regularly at 2 months interval or you took their informed signed, consent, enrol them, ask them to report regularly and do the electrolyte levels, mention also the period of study)who were prescribed various diuretics formed the sample. The clinical diagnosis, baseline investigations were recorded. Data of all types of diuretics prescribed were used for studying interval of appearance of ADE; types of ADE and their relationship (if any) with dose, diagnosis and age. The diuretics prescribed were loop diuretics (furosemide 20 and 40 mg) and potassium sparing group (spironolactone 50 mg, amiloride 10mg). Furosemide + amiloride FDC. The inclusion criteria for the study was :-
A) OPD level treatment
B) One diagnosis
C) Normal baseline serum electrolyte (S. electrolyte) report,
D) Given diuretics and other drugs based on diagnosis.

The Exclusion criteria was

1. Patients who needed indoor management
2. Poly-diagnosis
3. Abnormal baseline electrolyte level
4. Patients prescribed other drug affecting S. electrolyte
5. Diabetes mellitus patients
6. Malabsorption syndrome
7. 7)Chronic diarrhoea / recent gastroenteritis
8. Hepatic/renal failure patients on drug therapy

The patient's clinical protocol was tracked for clinical review, investigations, prognosis as per physician's advice. The S. electrolyte report was noted at two month interval till 12 months. We also recorded the pharmacotherapy of S. electrolyte imbalance over our study period.

Results

The present study was conducted on 453 men of age 25-75 years as per inclusion criteria. The distribution of age and the diagnosis (renal edema, hepatic edema, hypertension, ischaemic heart diseases) is shown in Figure 1.

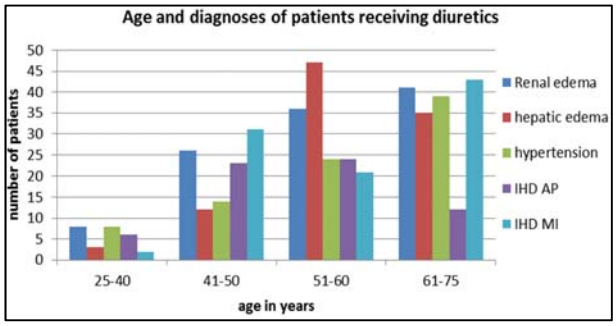

Fig 1: The distribution of age and diagnosis of patients receiving diuretics

Ischaemic heart disease
* Angina pectoris
** Post MI (conservative therapy)

Among the patients given diuretics, there were least number (27-6%) of patients in 25-40 yrs, and maximum (170-37.5%) in group 61-75 yrs. As per diagnosis, there were patients of renal edema -109 (nephritis 24%), hepatic edema-97(cirrhosis-21.4%), hypertension (mild)-85(7%), angina pectoris-65(14.5%) and post-myocardial infarction, non-interventional (post MI) --97 (21.4%) patients.

The patients were prescribed spironolactone 50 mg BD in 93(20.5%), furosemide 20mg OD in 94(20.7%); 40 mg OD in 73 (16.1%), and furosemide + amiloride fixed dose combination (FDC) [20 mg +10 mg] OD in 193 (42.6%) cases ; The diagnosis of patients prescribed the above medicines is shown in figure 2.

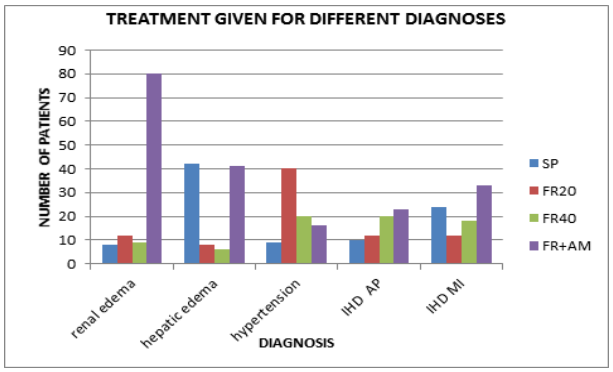

Fig 2: Diuretic treatment prescribed for different diagnoses
The serum sodium & potassium reports were considered for assessing the change in number of patients at different month intervals.

Table 1: Delayed expression of electrolyte imbalance with different treatments over a period of Twelve months

Type	Medicines	2 Month	4 M	6 M	8 M	10 M	12 M
HPRK	furosemide+Amiloride	●	●●	●			
	furosemide40 mg						
	furosemide 20 mg		★	★			★
	spironolactone						
HN	furosemide+Amiloride	●● ▼▼▼					
	furosemide40 mg		▼	▼	▼		
	furosemide 20 mg	■	■				
	spironolactone						
HK	furosemide+Amiloride						
	furosemide40 mg	▼▼▼	▼▼	▼▼	▼▼	▼	▼▼
	furosemide 20 mg	■					
	spironolactone						

HPRK -hyperkalaemia, HN- hyponatraemia, HK- hypolalaemia

Table 2: Number of patients showing electrolyte imbalance receiving different Medicines

Electrolyte change	Number of patient showing electrolyte imbalance				total
	Spiranolactone	furosemide 20 mg	furosemide 40 mg	Furosemide +Amiloride	
Hypokalaemia	0	1	12	0	13(2.9%),
Hyponatraemia	0	2	7	2	11(2.4%)
Hyperkalaemia	3	0	0	4	7(1.5%).
Total	3	3	19	6	31

Hypokalaemia: was seen at 2months in 1 patient on spirolactone and in 3 patients each on furosemide 20 and 40 mg. At 4, 6 and 8 months 2 patients, on furosemide 40 mg therapy, reported hypokalemic. Hypokalaemia was also seen at 10 months in one patient and at 12 months in two patients on furosemide 40 mg therapy. Spiranolactone and

Furosemide+Amiloride did not induce hypokalaemia at any time interval.

Hyponatraemia: Low serum sodium was seen in one patients taking furosemide 20 mg, at 2 and 4 months interval. hyponatraemic at 2 months was found in 4 patients on Furosemide 40 mg therapy and in one patient each at 4,6 and 8 months. It was also detected in 2 patients on furosemide +amiloride therapy at 2 months interval.

Hyperkalaemia: was detected in three patients on spironolactone one each at an interval of two, four and six months. One patient at two months, two patients at four months and one patient at 6 months on furosemide + amiloride therapy showed hyper kalemia. Overall, electrolyte imbalance was observed in 31 (6.8%) patients, with hypokalaemia in 13 (2.9%), hyponatraemia in 11(2.4%) and hyperkalaemia in 7 (1.5%).

The ADE of diuretics as electrolyte imbalance in context of diagnosis was seen in total 31 patients except angina pectoris (0), as shown in table 4.

Table 3: Number of patients showing electrolyte imbalance having different diagnoses

Electrolyte change	Diagnosis					Total
	Hepatic edema	Renal Edema	Hyper-tension	Angina pectoris	Post MI	
Hypokalaemia	5	4	2	0	2	13 (42%)
Hyponatraemia	2	6	1	0	2	11 (35.5%)
Hyperkalaemia	**3**	2	0	0	2	7 (22.5%)
Total	10 (32.2%)	12 (38.7%)	3 (9.7%)	0	6 (19.4%)	31 (100%)

Table 3 depicts the total number of patients showing electrolyte imbalance (31) and its occurrence among different diagnosis. Ten patients (32.2%) of hepatic edema showed electrolyte imbalance, 12 patients (38.7%) of renal edema, three patients (9.7%) of hypertension and six (19.4%) of Post MI patients. Hypokalaemia was maximum in five patients were of Hepatic edema. Hyponatraemia was maximum in six patients of renal edema while hyperkalaemia was seen in three of Hepatic edema patients. Overall electrolyte imbalance in hepatic edema was found in 10(32.2%), in renal edema-12 (38.7%), in hypertension-3 (9.7%), and in post MI - 6 (19.4%) patients. No p [atient of angina
Showed any electrolyte imbalance.

The age wise distribution of electrolyte imbalance as shown in the figure 3 indicates that in the group 61-75 there were maximum number of patients.

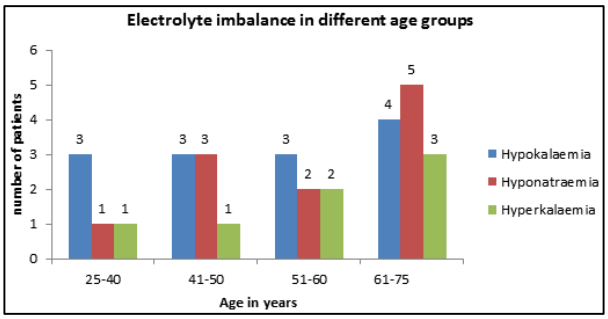

Fig 3: Electrolyte imbalance in different age groups after long term diuretics.

All the age groups have shown S. Electrolyte imbalance. In group 25-40 years there were 5 patients (16.1%), while in group 61-75 years, there were 12 (38.7%) patients.

Discussion

Diuretics are frequently prescribed drugs in several medical conditions. The Pharmaco-therapy may be of short or long duration which may later cause serious ADE in the form of S. electrolyte imbalance, affecting vital cardiac function. Monitoring these biochemical changes should be the aim of ethical therapeutics. There are no data about the interval between starting diuretic treatment and the appearance of electrolyte imbalance. Moreover reports on the complex relationship between the type of diuretic, its dose, and type of electrolyte imbalance, clinical diagnosis, and age vulnerability are lacking. The present study is an effort to document such information so that even marginal detection of ADE, would be considered for advocating prompt therapy to reduce morbidity and mortality. Even though the S. electrolyte levels are within physiological limits, bordering on the higher side, regular bimonthly estimation may give an early warning of the declining, static, gradual or rapidly increasing concentration. In the beginning, marginal changes may be asymptomatic or clinically undetectable, a situation of clinically prognostic dilemma, but short spaced investigation may signal the risk, and timely treatment at this stage may prevent further complications.

In this study 453 eligible adult males,between 25-75 yrs with different diagnoses were enrolled. Our results indicate that diuretics are needed more in upper age group. It is observed that patients with high normal S. potassium level- where is the data in results? (5 mEq/dl) at baseline investigation were prescribed Furosemide + Amiloride combination. This is in agreement with the principles of preventing hyperkalaemia.[1] There are multiple indications of diuretics including lifesaving one. Among group of diuretic prescription, patients suffering from renal edema (nephritis) and those in the age group of 61-75 years were maximum. It shows the trend of renal diseases being prominent in elderly which agrees well with reports by other authors [2].

Although the mechanism of action (MOA) of various diuretic is different, the ultimate effect is to eliminate sodium and water load; reduce extracellular fluid volume and vascular edema[1]. Furosemide is highly potent loop diuretic, site of action being ascending limb of loop of Henle, where it inhibits Na^+- K^+- $2Cl^-$ symport, may cause hypokalaemia and hyponatraemia [1], whereas spironolactone and amiloride are weak diuretics, but both are potassium sparing, so hypokalaemia does not occur. Spironolactone by MOA is a mineralocorticoid receptor (MR) antagonist, acts on late distal tubule. Amiloride interacts with the Na+- K+- H+ transport mechanism at distal convoluted tubule and collecting duct[1]. However potassium sparing diuretics may lead to hyperkalaemia [1, 2]. These electrolyte alterations which have multiple adverse functional cardiac effects [2], may lead to

extended indoor stay, more cost of therapy and also risk of mortality. Moreover the problem with these changes is that in few patients they are asymptomatic and undetectable clinically -- a silent risk. Therefore fair information of time lag in expression of the electrolyte changes, the type of electrolyte disorder, which patients by age and diagnosis are vulnerable for these ADE is very vital for the treating physician.

In the present study S. electrolyte imbalance (total 6.8%) was seen as hypokalaemia (2.9%), hyponatraemia (2.4%) and hyperkalaemia (1.5%). At two months, Hypokalaemia was evident in patients taking furosemide 20mg and more with 40 mg, showing the dose dependent risk potential.

Hyponatraemia was observed with furosemide 20 mg and 40 mg with dose dependent effect; and also with furosemide + amiloride FDC.

Hypokalaemia and hyponatraemia did not show similar inter patient incidence or related diagnosis, which may be due to individual variable state of electrolyte elimination kinetics [1].

Hyperkalaemia in furosemide + amiloride FDC treated group showed early electrolyte imbalance at two months interval, warrants caution; it may be possible that few or more of these ADE have occurred still earlier, suggesting investigations at shorter period. S. electrolyte reports at later intervals from 4 to 10 months also show all three ADE with variable pattern.

At twelve months ADE is found as hypokalaemia in furosemide 40 mg dose and hyperkalaemia in spiranolactone, which suggests not to overlook the possibility of delayed S. electrolyte imbalance. It is noteworthy that the total ADE of furosemide are three with 20 mg dose, and 19 with 40 mg dose, a dose dependent effect; this draws the attention to titrate dose cautiously so as to avoid ADE. Hyperkalaemia is the principle risk of spironolactone which can be life threatening[1]. Overall the S. electrolyte imbalance (6.8%) although showed variable pattern with reference to time interval, age and diagnosis, a chronological relation of diagnosis and ADE could be established. In renal edema ADE was seen in 12 (38.7%), hepatic edema in10 (32.3%), post MI in 6 (19.3%), and hypertension in 3(9.7%) but none from angina pectoris group. However the incidence of hypokalaemia was most (42%), followed by hyponatraemia (35.5%), and hyperkalaemia (22.5%) The diuretics interact with pathology (drug-disease interaction) of renal edema (nephritis) that involve reduced GFR, alteration in electrolyte kinetic; of hepatic edema (cirrhosis) causing hyper-aldosteronic state; of post MI causing haemodynamic alteration and hypertension affecting renal, vascular elements and extracellular fluid volume derangement[3]. All the age groups have shown ADE as electrolyte imbalance; the finding regarding upper age group suggest that due to declining physiological function of renal, gastro-intestinal, hepato-biliary systems the ADE in geriatric age are maximum, corroborates with other reports[4]. Surprisingly no patient of angina pectoris group showed any electrolyte imbalance due to diuretics.

Conclusion

In the present study we made an attempt to find out the adverse effects of diuretics pursued over 12 months (spiranolactone, furosemide and amiloride) prescribed to 453 patients of 25-75 yrs age. Most patients were of age group 61-75 yrs (37.5%) and maximum were suffering from renal edema (24%). The diagnostic indications were renal edema, hepatic edema, hypertension, and ischaemic heart disease (stable angina pectoris, post myocardial infarction).The diuretic preferred most was furosemide+amiloride combination (42.5%). The electrolyte imbalance observed (total 6.8%) were hypokalaemia (42%), hyponatraemia (35.5%) and hyperkalaemia (22.5%).The early adverse effect at 2 month interval found, was hyponatraemia in 7(22.6%), hypokalaemia in 4(13%), and hyperkalaemia in 1 (3.2%). At time interval of 12 months, hypokalaemia (6.4%) and hyperkalaemia (3.2%) were observed. At 4-10 months, electrolyte imbalance was seen in similar way with variable pattern. Electrolyte imbalance was found mostly in patients of renal edema (38.7%), and least of hypertension (9.6%). No adverse effects were seen in patients of angina pectoris group, but it does not mean that in these patients ADE may not occur. In nutshell the electrolyte imbalance due to diuretics may occur at any time, irrespective of diagnosis or age, drawing the attention to meticulously plan for prolonged or lifelong therapy. Repeated short interval investigations correlated with age, symptoms, clinical examination and diagnosis should be the aim of modern ever-developing field of medical science.

References

1. Regulation of renal function and vascular volume. In: Goodman and Gillman.The Pharmacological Basis of Therapeutics, Bruton, Chabner, Knollman (Ed) 2011; 671-700.
2. Aging and disease. In: Davidson principle and practice of Medicine, Walker, Colledge, Ratson, Penman (Ed). Churchille Livingstone, Elsavier, 2014, 166-178.
3. Robbins Basic Pathology, Vinaykumar, Abbas, Aster (Ed), Reed Elsevier India private limited, p: pathogenesis nephritis 518, cirrhosis of liver 617, hypertension 2014, 333, 375-77.
4. Geriatric physiology- Aging. In Harrisons Principle and Practice of Internal Medicine. Lango, Fauci, Kasper, Hauser, Jameson, Loscalzo (Ed), Mac Graw hills, 2012; 1:562-69.