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DIURETICS INTERACTIONS WITH MEDICATIONS USED IN THE MANAGEMENT OF CONGESTIVE HEART FAILURE AND OTHER CO-MORBID CONDITIONS: AN INDICATION FOR CONSTANT DRUG THERAPY MONITORING AND VIGILANCE

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ABSTRACT

Background: Many patients are worried receiving medications that have adverse drug interactions that will further affect their health status. **Objectives:** The objectives were to assess potential interactions between three classes of diuretic with other medications and to evaluate the potential clinical outcomes as well as to identify patients that may require constant monitoring and vigilance. **Methods:** The cross-sectional and prospective study involve the evaluation of drug interaction between diuretics and other medications using online drug interaction software checkers developed by Medscape.com, Drug.com, Drugbank.com and Epocrates online. **Results:** The proportion of patients recommended for diuretics among the middle aged adult was 41.7%, 34.3% and 20.0% for loop, K-sparing and thiazide diuretics respectively. Drugs co-used with loop diuretic when compared with the total number of such drugs in the entire study were as high as 75% each for atorvastatin, nifedipine, captopril and carvedilol; and as low in thiazide combinations with amiodarone (4.8%), $CaCO_3$(6.4%), calcitriol (7.5%) and allopurinol (13.6%). Out of 23 paired interactions that occurred between loop diuretic and other medications, 21(91.3%) were single interaction while 2(8.7%) were double interactions. With K-sparing diuretic interactions and other medications 18(90.0%) were single while 1(5.0%) each were double and quartet interactions respectively. In thiazide diuretics single interaction were 19(90.5%) while double and triple interactions were 1(4.76%) each. Pharmacokinetic versus pharmacodynamics interactions were 49(10.7%) versus 407(89.3%); 56(17.7%) versus 260(82.3%); and 8(12.5%) versus 56(87.5%) in loop, K-sparing and thiazide diuretics respectively with an overall Pharmacokinetic and pharmacodynamics interactions of 113(13.5%) versus 723(86.5%) respectively. A total of 19 potential outcomes resulting from 124 drug pairs, which accumulated to 1944 outcome cases were observed. Antagonism to potassium levels were the highest being 546 (28.1%). Others are increased risk of hyperkalemia 228(11.7%), risk of hypokalemia 16(0.8%), risk of hypotension 486(25.0%), risk of QT prolongation 2(0.1%), agents whose effects/levels is decreased by diuretic 120(6.2%), risk of SIADH 2(0.1), increase risk of adverse effects 88(4.5%) while risk of nephrotoxicity 26(1.3%), risk of decrease in the therapeutic effects/efficacy of diuretic 35(1.8%) and agents whose effects/therapeutic efficacy may be increased 190 (9.8%) may be potentially present. Combinations requiring monitoring K-levels accounted for 790 (41.3%). BP monitoring may be required in 486(25.4%) cases while downward and upward dosage adjustment of interacting drugs may be necessary in 289(15.1%) and 185(9.7%) cases respectively. Similarly diuretic upward and downward dosage modifications may be required in 36(1.9%) and 17(0.9%) cases respectively. **Conclusion:** Several potential drug interactions may be present in CHF Patients on diuretics with co-morbid diseases requiring medications. This calls for the need to keenly monitor all medications used by CHF patients as potentially lethal interactions may be present.

KEYWORDS: Diuretic interactions, potassium sparing diuretic, loop diuretic, thiazide diuretic, Furosemide, Spironolactone, Congestive Heart Failure.

INTRODUCTION

Diuretics are medications cause diuresis thereby removing electrolytes like sodium and chloride from the body in the urine, with the sodium and chloride in turn drawing excess water from the body. The most common ones often employed in therapy are the loop diuretics, which act at the loop of Henle; thiazide diuretics, which act at the distal convoluted tubules in the kidneys; the potassium-sparing diuretics reduce sodium reabsorption at the distal tubule and decrease potassium secretion. Other diuretics like carbonic anhydrase inhibitors increase the excretion of sodium, potassium, bicarbonate and water from the renal tubules and the osmotic diuretics.[1]

Diuretics are used alone or in combinations with other medications as adjunctive therapy in many conditions to control edema associated with congestive heart failure (CHF) using loop diuretics, nephrotic syndrome, cirrhosis of the liver using aldosterone antagonist like spironolactone.[1, 2] and corticosteroid and estrogen therapy and in edema associated with renal related diseases or dysfunction. They may be used alone as therapeutic agents to treat hypertension[3] or in combination with other antihypertensive drugs to treat more severe forms of hypertension. Those in the class of carbonic anhydrase inhibitors have been used as adjunctive treatment of chronic simple (open-angle) glaucoma and secondary glaucoma.

Diuretics are one of the mainstay therapy used in the management of CHF since the illness is associated with volume overload.[4] The trio of loop, thiazide and potassium sparing diuretics are often recommended for patients so as to achieve definite clinical outcomes. Furosemide is one of the loop diuretics that are used in practice for the removal of excess fluid overload associated with diseases like CHF, liver cirrhosis, CKD and so on. The agent owned its therapeutic relevance in CHF conditions due to reversible inhibition of sodium, potassium and chloride ion co-transporter at the thick ascending loop of Henle thereby causing a reduction in Na and Cl reabsorption with increased diuresis.[5] Furosemide decrease wedge pressure because of its action in dilating renal and venous vessels since it enhance in prostaglandin synthesis. Some loop diuretics, particularly torasemide and bumetanide, which have higher bioavailability profiles than furosemide from oral route may be better in effectiveness than furosemide.[6]

Thiazide or thiazide like agents like chlorothiazide, chlorthalidone, metolazone and indapamide shared similar action and find applications in CHF since they cause inhibition of Na-Cl transporter at distal nephron.[7] Thiazides have been reported to cause decrease in peripheral resistance[8] while agent like metolazone, a thiazide-like compound appeared superior in potency to some thiazides and even retain its effectiveness even when there is decrease in glomerular filtration rate.

Both loop diuretic and thiazide-like diuretics cause side effects of electrolyte imbalance such as of hypokalaemia, hypomagnesaemia, hypercalcaemia (thiazide), hypocalcaemia (loop), hyponatraemia, and hyperuricaemia.[7] In contrast to this, potassium-sparing diuretics like amiloride, spironolactone and triamterene which act via inhibition of mineralocorticoid receptor or its effectors at distal nephron cause hyperkalaemia side effects with spironolactone causing additional gynecomastia.[7]

Potassium-sparing diuretics particularly those that have the ability to antagonize aldosterone receptor such as spironolactone or eplerenone have found application in patients with CHF because they can act at the cortical collecting duct to reduce sodium and water absorption and increase hydrogen ions. When combined with other diuretics, they can correct or prevent potassium deficiency and may significantly reduce the deleterious effects of aldosterone on the cardiovascular system. However, they require frequent monitoring in order to prevent hyperkalaemia. It is recommended to be avoided in heart failure patients with renal failure if the baseline potassium level is more than 5 mmole/L.

Loop diuretics is the most commonly used diuretics when compared with thiazide diuretics with metolazone and potassium-sparing diuretics due to their most potent natriuretic action but potassium sparing diuretics is efficacious in improving the long-term prognosis in symptomatic HF patients while thiazide-like diuretics in CHF are used to overcome diuretic resistance.[7] Thiazides when combined with loop diuretic can avoid the need for parenteral administration of a loop diuretic in both CHF and end stage renal failure.[9,10] An aldosterone antagonist, like spironolactone**,** is sometimes also added to augment the diuresis and conserve K^+.[10]

Loop diuretics, such as furosemide and others are potent diuretics that act on the loop of Henle segment of the renal nephrons[10] and find usefulness in relieving pulmonary oedema due to left ventricular heart failure, oedema and oliguria in renal failure. Loop diuretics block the chloride pump, affecting the reabsorption of chloride and sodium. Furosemide-induced electrolyte disturbances may cause hypokalemia. The outcome of this can increase the risk of cardiac arrhythmia or may even lead to death when combined with drugs that prolong the QT interval.

Potassium-sparing diuretics such as amiloride and spironolactone act on the distal tube segment of the nephron. They are not as potent as loop diuretics but are useful in those at risk of hypokalaemia (patients on digoxin or taking anti-arrhythmiac drugs). Potassium-sparing diuretics are often used as adjuncts to thiazides or loop diuretics. When given with thiazides, they counteract the increased glucose and uric acid levels associated with thiazide diuretic therapy.[11]

Diuretics interact with many drugs resulting in diverse clinical outcomes such as increase potassium loss (with corticosteroids), intoxication (with lithium and digoxin) or hypotension (with potentiate blood pressure lowering agents), loss of diabetic control (with anti-diabetic agents), nephrotoxic and ototoxic effects (with aminoglycosides) and so on.[11,12]

Many patients are worried receiving medications that have drug interactions that will adversely affect their health[13]; which justify the needs to study diuretic potential interactions with other medications.

AIM AND OBJECTIVES

The objectives were to assess potential interactions between some diuretics and other medications and to evaluate its degree, potential clinical outcomes as well as to identify patients that may require constant monitoring and vigilance.

MATERIALS AND METHODS

The study was conducted at the University of Maiduguri Teaching Hospital, Maiduguri, Borno State; which is situated at the North-East zone of Nigeria. The Tertiary hospital runs several clinics including Cardiology Clinics. The cross-sectional and prospective study involves the evaluation of drug interaction involving diuretic and other medications prescribed for patients with congestive heart failure. Online drug interaction software checkers developed by Medscape.com, Drug.com, Drugbank.com and Epocrates were used complimentarily to evaluate diuretic combinations with other prescriptions ordered for individual patient. The CHF Patients were sampled from out-patients and in-patients departments as well as during patients' clinic visits.

RESULTS

The proportion of patients recommended for diuretics among the middle aged adult was 41.7%, 34.3% and 20.0% for loop, K-sparing and thiazide diuretics respectively. For patients below 20 years, these corresponding values are 13.7%, 5.5% and 30.0% respectively while in adults above 50 years; the values are 34.0%, 39.3% and 50.0% respectively (Table 1)

Drugs co-used with loop diuretic were in high proportions among several patients when compared with the total number of such drugs used in the entire study. These proportions were as high as 75% for atorvastatin, nifedipine, captopril and carvedilol (Table 2).

Out of 23 paired interactions that occurred between loop diuretic and other medications, 21(91.3%) were single interaction each while 2(8.7%) were double interactions each. Similarly, 18(90.0%) of potassium sparing diuretic interactions with other medications occurred as single interaction while double and quartet interactions respectively occurred in 1(5.0%) case each. With thiazide diuretics the proportions are single interaction 19(90.5%), double and triple interactions 1(4.76%) each (Table 3).

Pharmacokinetic and pharmacodynamics interactions were 49(10.7%) and 407(89.3%) respectively for loop diuretics; 56(17.7%) and 260(82.3%) respectively for potassium sparing diuretics; and 8(12.5%) and 56(87.5%) respectively for thiazide diuretics. The overall Pharmacokinetic and pharmacodynamics interactions in the study were 113(13.5%) and 723(86.5%) respectively (Table 4).

A total of 19 potential outcomes resulting from 124 drug pairs, which accumulated to 1944 cases were observed using several drug interaction evaluators. Interactions that antagonizes potassium levels were the highest being 546 (28.1%) while those that constitute the lowest were interactions that may increase the risk of SIADH 2(0.1) or cause QT prolongation 2(0.1%) or increased the metabolism of diuretic 1(0.05%) or decrease their metabolism 11(0.6%) or decrease the excretion of diuretic 13(0.7%) or those that may synergistically decrease K levels and cause hypokalemia 16(0.8%). Other clinically significant interaction outcomes of importance are agents that may increase the risk of hypotension 486(25.0%), or increase the risk of hyperkalemia 228(11.7%); agents that diuretic may increase their effects/therapeutic efficacy 190 (9.8%); agents whose effects/levels is decreased by diuretic 120(6.2%).Agents that diuretic may decrease their excretion rates and agents that may increase risk or adverse effects were 88(4.5%) each while risk of nephrotoxicity 26(1.3%) and agents that decrease the therapeutic effects/efficacy of diuretic occurred in 35(1.8%) cases (Table 5).

We identified nine (09) areas requiring interventions in the study. Combinations requiring monitoring K-levels accounted for 790 (41.3%). BP monitoring may be required in 486(25.4%) cases while downward and upward dosage adjustment of interacting drugs may be necessary in 289(15.s1%) and 185(9.7%) cases respectively. Similarly diuretic upward and downward dosage modifications may be required in 36(1.9%) and 17(0.9%) cases respectively (Table 6).

DISCUSSION

CHF is a chronic cardiovascular disease that affects all age strata and requiring several medications for its management including diuretics. Co-prescription of diuretic agents and other medications is common and often unavoidable in practice. While most of such combinations may have beneficial effects, many may also have some adverse consequences due to other patients' presenting conditions. In this study, the ratio of occurrence of diuretic used as a component of medications in the management of patients with CHF before and after the age of 40 years is 1:1.1. Diuretics used by patients with CHF occurred in all age bands but the use of loop diuretics is higher than K-sparing and thiazide diuretics. K-sparing diuretics are often combined with loop diuretic in practice in order to conserve K losses.[10] The high proportion of loop diuretic used in this study compared to other forms of diuretics is attributed to their high ceiling nature since CHF is characterized by generalized edema.

Drug combinations with diuretics are diverse but antihypertensive agents constitute the highest combination. This is expected since hypertension is one of the major risk factors for CHF while CHF is one of the complications of hypertension. Other combinations

such as statins, anti-arthritis, anti-platelets and etc are essential combination and a reflection of the extent of co-morbidity on patients with CHF.

Several drug pairs with diuretics showed various kinds of interactions in the study. Drug pairs that have shown mono-interaction were the highest in the study. For instance out of the 75 different types of drug pairs with diuretic that have shown interactions, single mode of interaction accounted for majority of the interactions while double interactions mode were seen a few cases although triple mode and quartet mode of interactions were each seen in one pair with diuretic (Table 3). Understanding the mode and number of interactions in a drug pair is important in resolving drug therapy problems during pharmaceutical care.

Among the outcomes identified in the study are the potential interactions caused by diuretics that will increase the serum concentrations of other drugs (particularly agents like aspirin, digoxin, and atorvastatin), which imply an increased therapeutic effects as well as toxicities of these drugs. The effects may be more on agents with narrow therapeutic range like digoxin and on agents that may prolong QT interval like. Conversely, two agents combined with diuretics in the study were observed to show potential interactions with diuretics that will increase the serum levels of such diuretics. These agents are digoxin and amiodarone effects on hydrochlorothiazide through basic cationic drug competition for renal tubular clearance. Aspirin may interact with diuretics like furosemide and spironolactone through pharmacodynamics antagonism to decrease their therapeutic efficacies, though these interaction pairs were observed in few patients.

Some positive outcomes were observed from our interaction checks in eighteen drug paired with various diuretics. For example, diuretic may increase the therapeutic efficacies of those interacting drugs. Agents affected mostly are atenolol, carvedilol, hydralazine, nifedipine, amlodipine, losartan and lisinorpril etc, which are used primarily to control hypertension in most patients. These seemingly advantage notwithstanding, the combination can also present negative outcomes such as hypotension. Therefore, with keen monitoring of blood pressures, the interaction of this kind can be gainfully explored.

On the contrary, there are also several drug pairs with diuretic that may lead to decrease in therapeutic efficacies or effects of interacting drugs. The mechanism is based on either increased metabolism or increased excretion as well as antagonisms, while the basis for the decrease serum concentrations of most of those affected drugs are not quite clear. Examples of drugs in this category are the statins whose metabolism is increased by spironolactone, and agents like colchicine, clopidogrel, nifedipine, rifampicin, whose serum concentration is decreased by spironolactone. Although spironolactone decreases the serum concentration of nifedipine, furosemide on the contrary may increase it by decreasing its excretion rates. These agents would also need to be monitored and their dosage adjustments may be required to achieve the desired therapeutic benefits.

Three major outcomes in potassium concentrations were observed from drug-drug interactions between diuretics and other interacting agents. In about twenty pairs, drug antagonism were observed due to some diuretics like loop and thiazide diuretics decreasing serum concentrations of potassium while the interacting drugs may increase it. The net effects from this type of interaction can lead to hypokalemia, hyperkalemia or no change depending on the existing serum levels of patients, potassium intake and use of other medication that may cause electrolyte changes. There were two pairs that may result to hypokalemia and six pairs with diuretics that may lead to hyperkalemia. Single diuretic use alone has been reported to cause either hyponatraemia, hypomagnessemia, hypercalcaemia or hypocalcaemia, hyperkalaemia or hypokalaemia, and etc depending on the type of diuretic in question[(7)]. All these agents require monitoring.

Risk of hypotension was observed in 26 drug pairs while two agents paired with diuretic may lead to nephrotoxicity. The risk of severity of adverse effects may be present in 6 drug pairs while hypersensitivity reaction may occur in one drug pair in the study.

Adverse drug interaction defined as an interaction between one or more coadministered medications that results in the alteration of the effectiveness or toxicity of any of the coadministered medications is the most worrisome outcome of drug interactions. These outcomes may be under estimated in this study since interactions occurring between other drugs pairs other than diuretic were not evaluated in the study and there are several of such possibilities. Minimizing the risk for drug interactions should be a goal in drug therapy because interactions can result in significant morbidity and mortality.

Several clinical interventions may be required depending on the outcome of monitoring. For instance, few cases of interactions may require an upward or downward dose modification of diuretics or the interacting agents. With ongoing use adjustments like, alternate day or even less frequent dosing like 1–2 times weekly have been suggested ideal for some patients depending on other considerations.[14] Majority of the intervention require in the study is those relating to potassium levels as potential hypokalaemia and hyperkalaemia are likely to occur. Both conditions can have deleterious effects on the kidney. The renal status and heart status of some patients deserve to be monitored in some cases. Close monitoring of plasma electrolytes, renal function, and clinical response such as blood pressure, body weight, and diuresis are generally required when diuretics are used

with other agents.[14] According to some recommendations, clinical symptoms of diuretic use such as hyponatraemia can when occurred in any patient or even after prolonged treatment and in elderly people should be monitored for signs and symptoms like lethargy, dizziness or vomiting and should have their electrolytes and renal function measured.[15]

In many patients in this study, ACEIs were observed combined with potassium sparing diuretic with potential hyperkalaemia outcomes, thereby necessitating the need for close and regular monitoring of renal function and electrolytes is indicated. The dose of spironolactone is best kept below 25 mg daily and special attention must be paid on high risk patients such as older people, and renal or cardiac dysfunction patients. High risk patients of experiencing hyperkalaemia resulting from medication interactions involving diuretics are advised to avoid foods rich in potassium such as bananas, orange juice and melons and to avoid use of salt substitutes or other products that contain potassium.[16,17]

Table 1: Age of Patients on Diuretic Medications as Component of CHF Drug Management.

Age Distribut-ion	Frequen-cy N (%)	Loop diuretics		K-sparing diuretics		Thiazide diuretics		TOTAL Used N (%)
		Used N (%)	Unused N (%)	Used N (%)	Unused N (%)	Used N (%)	Unused N (%)	
0.0-10.0	19 (8.3)	16 (9.5)	3 (5.0)	0 (0.0)	19(12.3)	6 (30.0)	13 (6.3)	22 (8.4)
10.1-20.0	9 (3.9)	7 (4.2)	2 (3.3)	4 (5.5)	5 (3.2)	0 (0.0)	9 (4.3)	11(4.2)
20.1-30.0	25 (11.0)	18(10.7)	7 (11.7)	8 (11.0)	17(11.0)	0 (0.0)	25(12.0)	26(10.0)
30.1-40.0	52 (22.8)	45(26.8)	7 (11.7)	17(23.3)	35(22.6)	3 (15.0)	49(23.6)	65(24.9)
40.1-50.0	35 (15.4)	25(14.9)	10(16.7)	8 (11.0)	27(17.4)	1 (5.0)	34(16.3)	34(13.0)
50.1-60.0	47 (20.6)	27(16.1)	20(33.3)	16(21.9)	31(20.0)	7 (35.0)	40(19.2)	50(19.2)
60.1-70.0	29 (12.7)	21(12.5)	8 (13.3)	12(16.4)	17(11.0)	2 (10.0)	27(13.0)	35(13.4)
70.1-80.0	12 (5.3)	9 (5.4)	3 (5.0)	8 (11.0)	4 (2.6)	1 (5.0)	11 (5.3)	18 (6.9)
TOTAL (%)	228 (100)	168 (100)	60 (100)	73 (100)	155 (100)	20 (100)	208 (100)	261 (100)

Table 2: Drugs used by CHF patients and the proportions co-administered with diuretics.

Class of drugs	Drug name	No. used in the study	proportion of drugs co-used with diuretics		
			Loop n (%)	K-sparing n (%)	Thiazide n (%)
Beta-blocker	Carvedilol	86	65 (75.6)	56 (65.1)	4 (4.7)
	Atenolol	27	19 (70.4)	2 (7.4)	2 (7.4)
Centrally acting	Methyldopa	8	5 (62.5)	0 (0.0)	2 (25.0)
ACEI	Lisinopril	139	95 (68.3)	42 (30.2)	8 (5.8)
	Captopril	28	21 (75.0)	10 (35.7)	8 (28.6)
ARB	Losartan	40	23 (57.5)	10 (25.0)	2 (5.0)
Digoxin	Digoxin	71	51 (71.8)	45 (63.4)	3 (4.2)
Vasodilator	Hydralazine	3	2 (66.7)	1 (33.3)	0 (0.0)
CCB	Amlodipine	40	25 (62.5)	5 (12.5)	5 (12.5)
	Nifedipine	8	6 (75.0)	1 (12.5)	1 (12.5)
Anti-platelets	Vasoprin	31	22 (71.0)	13(41.9)	2(6.5)
	Clopidogrel	15	7 (46.7)	5 (33.3)	2 (13.3)
	Warfarin	21	14 (66.7)	16 (76.2)	1 (4.8)
Haematinics	Folic acid	49	32 (65.3)	7 (14.3)	0 (0.0)
	Ferrous sulfate	51	35 (68.6)	7 (13.8)	1 (2.0)
Statins	Atorvastatin	16	12 (75.0)	8 (50.0)	2 (12.5)
	Simvastatin	3	2 (66.7)	2 (66.7)	0 (0.0)
Anti-Tuberculosis	INH, PZI, RFP ETM	1(each)	1 (100.0)	0 (0.0)	0 (0.0)
Antacid	$CaCO_3$	47	31 (66.0)	5 (10.6)	3 (6.4)
	Calcitriol	53	35 (66.0)	8 (15.1)	4 (7.5)
Antiarrhythmic	Amiodarone	2	2 (100.0)	1 (50.0)	1 (50.0)
Anti-Gout	Colchicine	2	2 (100.0)	0 (0.0)	0 (0.0)
anti-arthritis	Allopurinol	22	15 (68.2)	5 (22.7)	3 (13.6)
Antidepressant	Amitriptyline	2	2 (100.0)	0 (0.0)	0 (0.0)

Key: INH=isoniazid; PZI=pyrazinamide; RFP=rifampicin; ETM=ethambutol; $CaCO_3$=calcium carbonate; ARB=angiotensin receptor blocker; ACEI=angiotensin converting enzyme inhibitor

Table 3: Some Specific Drugs Interaction with Diuretics.

Drug Interactions (no. of users)	No. of interaction (Loop diuretics)		No. of interaction (K-sparing)		No. of interaction (Thiazide)		Total (%)
Diuretic-captopril	1	21	1	10	1	8	39
Diuretic-Lisinopril	1	95	1	42	-	8	145
Diuretic-losartan	1	23	1	10	1	2	35
Diuretic-Carvedilol	1	65	1	56	1	4	125
Diuretic-spironolactone	1	61	-	-	1	4	65
Diuretic-bendro	1	4	1	4	-	-	8
Diuretic-HCT	1	4	1	0	-	-	4
Diuretic-Furosemide	-	-	1	61	1	8	69
Diuretic-nifedipine	1	6	-	-	1	1	7
Diuretic-Amlodipine	1	25	-	5	1	5	30
Diuretic-$CaCO_3$	1	31	1	5	1	3	39
Diuretic-Calcitriol	-	-	-	-	1	4	4
Diuretic-Digoxin	2	102	4	180	3	9	291
Diuretic-methyldopa	1	5	-	-	1	2	7
Diuretic-Hydralazine	1	2	-	-	-	-	2
Diuretic-Atenolol	1	19	1	2	1	2	23
Diuretic-Aspirin	2	44	2	26	2	4	74
Diuretic-Clopidogrel	-	-	-	-	-	-	-
Diuretic-Warfarin	1	14	1	16	1	1	31
Diuretic-Atorvastatin	-	-	1	10	-	-	10
Diuretic-Colchicine	1	2	1	0	-	0	2
Diuretic-Amiodarone	1	2	1	1	1	1	4
Diuretic-amitriptyline	1	2	-	0	1	0	2
Diuretic-Allopurinol	1	15	1	5	1	3	23
Diuretic-Folic acid	1	32	-	-	1	0	32
TOTAL	23	574	20	433	21	69	1076

Table 4: Specific types of diuretic-drug interactions.

Drug Interactions	Loop diuretics		K-sparing diuretics		Thiazide diuretics		Total
	Pharmacokinetic	Pharmacodynamic	Pharmacokinetic	Pharmacodynamic	Pharmacokinetic	Pharmacodynamic	
Diuretic-captopril	0	21	0	10	0	8	39
Diuretic-Lisinopril	0	95	0	42	0	8	145
Diuretic-losartan	0	23	0	10	0	2	35
Diuretic-Carvedilol	0	65	0	56	0	4	125
Diuretic-spironolactone	0	61	-	-	0	4	65
Diuretic-bendro	0	4	0	4	-	-	8
Diuretic-HCT	0	4	0	4	0	0	8
Diuretic-Furosemide	-	-	0	61	0	8	69
Diuretic-nifedipine	6	0	0	0	0	1	7
Diuretic-Amlodipine	0	25	0	0	0	5	30
Diuretic-$CaCO_3$	0	0	0	0	4	0	4
Diuretic-Calcitriol	**	0	0	0	0	4	4
Diuretic-Digoxin	0	51	45	45	3	3	147
Diuretic-methyldopa	5	0	0	0	0	7	12
Diuretic-Hydralazine	2	0	0	0	0	0	2
Diuretic-Atenolol	0	19	0	2	0	2	23
Diuretic-Aspirin	0	22	0	0	0	0	22
Diuretic-Clopidogrel	**	0	0	0	0	0	0
Diuretic-Warfarin	14	0	0	16	1	0	31
Diuretic-atorvastatin	**	0	10	10	0	0	20
Diuretic-Colchicine	2	0	0	0	0	0	0
Diuretic-amiodarone	0	2	1	0	0	0	3
Diuretic-amitriptylin	2	0	0	0	0	0	2
Diuretic-Allopurinol	0	15	0	0	0	0	15

Diuretic-Folic acid	0	0	0	0	0	0	0
Diuretic-warfarin	14	0	0	0	0	0	14
Diuretic-INH	1	0	0	0	0	0	1
Diuretic-PZI	1	0	0	0	0	0	1
Diuretic-ethambutol	1	0	0	0	0	0	1
Diuretic-rifampicin	1	0	0	0	0	0	1
TOTAL (%)	49	407	56	260	8	56	
	456		316		64		836

Table 5: Clinical Outcome of Diuretic Interactions with Other Medications.

S/ no.	Potential effects of interaction of diuretics with other drugs	Drug-pairs affected	Total cases (overall)	Percentage (%)
1.	Agents that diuretics may increase their serum levels	4	60	3.1
2.	Agents that increase serum level or effects of diuretics	2	4	0.2
3.	Agents that decrease therapeutic efficacy/effect of diuretics	2	35	1.8
4.	Agents that diuretic increase its levels/therapeutic efficacy	18	190	9.8
5.	Agents whose effects/levels is decreased by diuretics	12	120	6.2
6.	Agents that antagonize K^+ levels when used with diuretic	20	546	28.1
7.	Agents that co-decrease K^+ level & cause hypokalemia risk	2	16	0.8
8.	Agents that co-increase K^+ level & cause hyperkalemia risk	6	228	11.7
9.	Agents that may increase the risks of hypotension	26	486	25.0
10.	Agents that may increase the risks of nephrotoxicity	2	26	1.3
11.	Agents that may cause increased risk of SIADH	1	2	0.1
12.	Agents that diuretic may cause QT-prolongation	1	2	0.1
13.	Agents that diuretics may increase their excretion rates	6	25	1.3
14.	Agents that diuretic may decrease their excretion rate	11	88	4.5
15.	Agents that may increase risk or severity of adverse effects	6	88	4.5
16.	Agents that may decrease the excretion of diuretics	1	13	0.7
17.	Agents that increased the metabolism of diuretics	1	1	0.05
18.	Agents that diuretics may decrease their metabolism	2	11	0.6
19.	Agents that cause risk of hypersensitivity reactions	1	3	0.15
	TOTAL	124	1944	100

Table 6: Intervention Required.

S/no.	Types of interventions required	Freq.	%
1.	combination requiring diuretic monitoring	80	4.2
2.	Combination requiring diuretic dose modification (upward)	36	1.9
3.	Combination requiring diuretic dose modification (downward)	17	0.9
4.	Combination requiring dosage modification (upward) of interacting drugs	185	9.7
5.	Combination requiring dosage modification (downward) of interacting drugs	289	15.1
6.	Combination requiring monitoring of K levels	790	41.3
7.	Combinations requiring BP monitoring	486	25.4
8.	Combinations requiring renal status monitoring	26	1.4
9.	Combinations requiring ECG monitoring of heart status	2	0.1
	TOTAL	1911	100

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