IJPSR (2017), Volume 8, Issue 8 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 11 January, 2017; received in revised form, 30 March, 2017; accepted, 27 May, 2017; published 01 August, 2017

INCIDENCE OF DIURETICS INDUCED ADVERSE DRUG REACTIONS IN AN INTENSIVE CARDIAC CARE UNIT OF A TERTIARY CARE TEACHING HOSPITAL

S. Vikas [1], M. Ramesh [2], Vanitha N. Rani [*3], P. Thennarasu [3] and G. Kannan [4]

Department of Pharmacy Practice [1], Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur - 522019, Andhra Pradesh, India.
Department of Accident and Emergency Medicine [2], Department of Pharmacy Practice [3], Faculty of Pharmacy, Sri Ramachandra University, Porur, Chennai - 600116, Tamilnadu, India.
Department of Pharmacy Practice [4], Acharya and B. M. Reddy College of Pharmacy, Bangalore - 560107, India.

Keywords:

Diuretics,
Adverse drug reactions,
electrolytes

Correspondence to Author:
Dr. N. Vanitha Rani

Assistant Professor,
Department of Pharmacy Practice, Faculty of Pharmacy,
Sri Ramachandra University
Porur, Chennai - 600116,
Tamilnadu, India.

E-mail: vanithak9@rediffmail.com

ABSTRACT: Objective: The present study was conducted to assess the incidence, causality and severity of diuretic induced Adverse Drug Reactions (ADRs). **Method:** 92 patients admitted in the intensive cardiac care unit and prescribed with diuretics were included and data on demographics, past medical and medication history, allergies to food/drugs, laboratory parameters, diuretics prescribed, side effects and ADRs were obtained. The causality of ADRs was assessed using Naranjo's and WHO's a causality assessment scale, the severity of ADRs using Hartwig and Siegel's scale. **Results:** 41 (44.6%) patients were prescribed with one diuretic, 38(41.3%) with 2 diuretics and 13 (14.1%) with 3 diuretics. 54 patients were prescribed with loop diuretics, a combination of loop and potassium sparing diuretics were given for32 patients; loop and thiazides for 5 and a potassium sparing diuretic for one patient. Of 40 (44%) patients with ADRs, 32 had one ADR, 7 had two ADRs and one patient had three ADRs. Naranjo's scale identified 25 ADRs as probable, 15 as Possible and none as unlikely or certain; WHO scale identified 22 ADRs as Possible and 18 as Probable. Hartwig's and Seigel's scale identified 28 ADRs as moderate, 09 as Mild and 03 as severe. Diuretics were continued for 30 patients and ADRs were managed by electrolyte replacement. Diuretics were withdrawn for 10 patients and potassium supplementation or a potassium sparing diuretic was given. **Conclusion:** This study suggests that diuretics induced ADRs could be minimized by early prediction of the symptoms developed by diuretics and assessing the laboratory abnormalities.

INTRODUCTION: Adverse drug reactions have a major impact on public health and are major cause of hospital admissions, reducing patient's quality of life and imposing a considerable financial burden on the health care systems.

QUICK RESPONSE CODE

DOI:
10.13040/IJPSR.0975-8232.8(8).3557-62

Article can be accessed online on:
www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (8).3557-62

World Health Organization defines an adverse drug reaction (ADR) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".

Adverse drug reactions (ADRs) are a major cause of hospital admissions, but recent data on the incidence and clinical characteristics of ADRs which occur following hospital admission, are lacking. The purpose of documenting adverse drug events is to prevent future injuries for patients. New adverse drug reactions are often discovered

when drugs are used in larger or in different populations than studied during initial clinical trials. Therefore, documentation and reporting becomes a crucial element in clarifying the side effect profile of a drug. But recent data on the incidence and clinical characteristics of ADRs which occur following hospital admission are lacking [1]. Chemically, diuretics are a diverse group of compounds that either stimulate or inhibit various hormones that naturally occur in the body to regulate urine production by the kidneys. Diuretics increase urinary excretion of water and electrolytes and are used to relieve edema associated with heart failure, nephrotic syndrome or hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are mainly used to treat cerebral edema, and also to lower raised intraocular pressure.

Side effects of diuretics have also been identified as a significant problem in recent large scale trials [2, 3]. Diuretics were frequently discontinued because of side effects. Generally, side effects of diuretic therapy are mainly due to the fluid and electrolyte imbalance induced by the drugs. Hyponatremia is an adverse effect of all diuretics [4]. The risk of hypokalemia, which may occur with both thiazide and loop diuretics, depends more on the duration of action than on potency and is thus greater with thiazides than with loop diuretics (when given in equipotent doses). Potassium sparing diuretics can cause hyperkalemia, thiazides and loop diuretics cause hypomagnesaemia [5]. This study was conducted to assess the incidence and prevalence of diuretic induced adverse drug reactions (ADRs) occurring in an intensive cardiac care unit (ICCU) of a tertiary care teaching hospital and to explore the casual relationship of the developed adverse drug reactions (ADRs) and their severity using appropriate assessment scales.

MATERIALS AND METHODS: The study was conducted for a period of 6 months in a multispecialty tertiary care teaching hospital in South India, with the approval of Institutional Ethics committee and the consent of the study population. 92 consecutive patients of either sex, aged above 18 years, admitted to the intensive cardiac care unit (ICCU), prescribed with diuretic medications to treat various cardiovascular complications were included in the study. Patients with severe pathological conditions which result in electrolyte imbalances (abnormalities) were excluded from the study. A specially designed proforma was used for collecting patient's information from the case records and by direct history interview of the patient. The data obtained included: patients demographics (age, sex, BMI), past medical and medication history, family history, previous allergies to food/drugs, social history, details of physical examination (blood pressure, pulse rate, respiratory rate), laboratory parameters [Electrolyte levels (sodium, potassium, magnesium, chloride); Renal profile (Blood urea nitrogen, uric acid levels, Creatinine concentration); Lipid profile (LDL, HDL, Triglycerides); Random blood glucose levels]; drugs prescribed, side effects and adverse drug reactions.

The adverse effects identified in the study population were assessed for their causal relationship with the diuretics prescribed using the Naranjo's causality assessment scale [6] and WHO causality assessment scale [7]. The severity of the adverse drug reactions was assessed using the Hartwig's Severity assessment scale [8]. The Naranjo's causality assessment scale contains a score value ≥ 9 indicated a definite causal relation between the drug and the ADR; 5-8 as indicated a probable relation; 1-4 indicated a possible relation and a score of ≤ 0 indicated an unlikely relation. Hartwig's severity assessment scale contains 7 levels. Level 01 and 02 indicates that ADR is mild, level 03 and 04 indicates that ADR is moderate and level 05, 06 and 07indicates that ADR is severe.

Statistical analysis: The data were collected and tabulated. All the parameters were entered in the MS-Excel 2007 and SPSS 16.0 was used for statistical analysis. The categorical variables were expressed as descriptive statistics. The effect of age, gender, number of diuretics prescribed, their doses, route of administration on the occurrence of ADRs were assessed using student 't' test. AP value of <0.05 was considered significant.

RESULTS: The study was conducted in 92 patients [60 (65.2 %) males and 32 (34.8%) females] admitted in the ICCU of a tertiary care teaching hospital, with various cardiovascular

complications, and prescribed with the diuretics. The patients were assessed for the incidence of adverse effects due to diuretic medications. The maximum number of patients in the study population were found to be in the age range of 61-80 years (46 patients; 50%); 13 patients were in the age range of 19-40 years (14.1%); 28 patients were in the age range of 41 - 60 years (30.4%). 5 patients (5.4%) patients were found to be in the age of more than 80 years. The mean age of study population was found to be 60.25 ± 15.34 years (**Table 1**).

TABLE 1: AGE AND GENDER WISE DISTRIBUTION OF STUDY POPULATION

Age (Years)	No of Patients (N)		Total No. of patients (N=92)	Percentage (%)
	Males (n=60)	Females (n=32)		
19 – 40	08	05	13	14.1
41 – 60	20	08	28	30.4
61 – 80	29	17	46	50.0
> 80	03	02	05	05.4

Of 92 patients, 118 (75.64%) patients received their diuretics by oral route and 12 patients (7.692%) received torsemide by intravenous route. In this study, 41 (44.6%) patients were prescribed with a single diuretic. 38(41.3%) patients were prescribed with a combination of 2 diuretics and 13 (14.1 %) patients were prescribed with a combination of 3 diuretics. Loop diuretics were prescribed for 54 patients (58.7%), of which 20 patients were prescribed with furosemide; 20 were prescribed with torsemide, and 14 patients were prescribed with a combination of furosemide and torsemide. A combination of loop diuretic and a potassium sparing diuretic was given for 32 patients, which included furosemide and spironolactone for 09 patients, torsemide and spironolactone for 13 patients, and furosemide, torsemide and spironolactone for 10 patients.

Loop diuretic was given in combination with thiazides for 5 patients, which included combinations of furosemide and metalazone, torsemide and metalazone, furosemide, torsemide and metalazone, Torsemide, metalazone and bumetanide, furosemide, bumetanide and spironolactone for one patient each. Only one patient was prescribed a potassium sparing diuretic spironolactone (**Table 2**).

TABLE 2: DIURETICS PRESCRIBED Vs ADRs

S. No	Diuretics prescribed	No patients (N=92)	No of patients with ADRs (n=40)
1.	Furosemide	20	05
2.	Torsemide	20	06
3.	Spironolactone	01	--
4.	Furosemide + Torsemide	14	07
5.	Furosemide + Spironolactone	09	05
6.	Torsemide + Spironolactone	13	09
7.	Furosemide + Torsemide + Spironolactone	10	04
8.	Torsemide + Bumetanide + Spironolactone	01	01
9.	Furosemide + Metalazone	01	01
10.	Torsemide + Metalazone	01	01
11.	Furosemide + Torsemide + Metalazone	01	--
12.	Torsemide + Metalazone + Spironolactone	01	01

Of the 90 patients in the study, ADRs were observed in 40 patients, of which 32 patients (80%) had a single ADR (either hyponatremia, hypokalemia or hyperkalemia), 07 patients (17.5%) developed two ADRs simultaneously, only one patient (02.5%) developed combination of three ADRs (hypokalemia, hyponatremia and hypochloremia). **Table 2** depicts the ADRs occurred following administration of diuretic medications in the study population. ADRs were found to be high in patients on torsemide + spironolactone combination (9 out of 13 patients), followed by furosemide + Torsemide (7 out of 14 patients), furosemide + spironolactone (5 out of 9 patients), furosemide + Torsemide + Spironolactone (4 out of 10 patients), toresemide (6

out of 20 patients), furosemide (5 out of 20 patients) and in those patients who were receiving other three drug combinations except for one patient on furosemide + torsemide + metalazone (**Table 2**).

Table 3 explains the relationship between the baseline characteristics of the patients and occurrence of adverse drug reaction. ADRs were identified in 24 patients (52.17%) in the age group between 61-80 years, 08 patients (20%) patients in the age group between 19-40 years, 07 patients (17.5%) in the age group between 41-60 years and only one patient (2.5%) of age greater than 80 years. There was no statistically significant association (P=0.05) between age and occurrence of ADRs in the study patients. Of the 40 patients with ADRs, 24 (60%) were males and 16 were females. There was no significant association (P= 0.36) between gender and the occurrence of ADRs in the study population. In the study, of the 41 patients on monotherapy of diuretics, 10 patients (25%) developed ADRs; 51 patients were on combination of diuretics, of which 30 patients (75%) developed ADRs. There was a statistically significant association (P=0.02) between the occurrence of ADRs and combination therapy of diuretics than the monotherapy of diuretics.

Of the 35 patients who were on normal dose of diuretics, 13 patients (37.14%) developed ADRs; of the 36 patients prescribed with moderately high dose of diuretics, 14 patients (38.8 %) developed ADRs; of the 21 patients who were prescribed with very high dose of diuretics, 13 patients (61.90%) developed ADRs. The percentage of ADRs increased with increase in the diuretic dosage but there was no statistical significance (P=0.607).

TABLE 3: BASELINE CHARACTERISTICS Vs ADRs

Characteristics	No of Patients receiving diuretics (N=92)	No of Patients developed ADRs (n=40)		Significance P
		n	%	
Age (Years)				
19-40	13	08	20	
41-60	28	07	17.5	0.06
61-80	46	24	60	
>80	05	01	2.5	
Gender				
Males	60	24	60	0.36
Females	32	16	40	
Therapy				
Monotherapy	41	10	25	0.02*
Combination	51	27	72	
Dose of Diuretic				
Normal dose	35	13	32.5	
Moderately high dose	36	14	35	0.607
Very high dose	21	13	35	

*P<0.05 was considered statistically significant

Based on the causality assessment of adverse drug reactions, by using naranjo's causality assessment scale, out of 40 ADRs identified in the study population 25 ADRs (62.5%) were found to be probable, 15 ADRs (37.5%) were Possible. No ADRs were classified as unlikely or certain in the study population (**Table 4**).

Based on the causality assessment of adverse drug reactions using WHO causality assessment scale, of the 40 ADRs developed due to diuretics, 22 ADRs (55%) were Possible, and 18 ADRs (45%) were Probable. No ADR was classified as certain, Unlikely, Conditional or Unclassifiable (**Table 5**).

Based on the Severity assessment of ADRs using Hartwig's Severity Assessment scale, of the 40 ADRs developed in the study population, 28 ADRs (70%) were found to be moderate, and 09 ADRs (22.5%) were Mild and 03 ADRs (7.5%) were classified as severe (**Table 6**).

TABLE 4: NARANJO'S CAUSALITY ASSESSMENT OF ADRS

S. No	Type of Adverse Drug Reaction	No of adverse drug reactions (N=40)	Percentage of ADRs (%)
1.	Definite	-	-
2.	Probable	25	62.5
3.	Possible	15	37.5
4.	Unclassifiable	-	-

TABLE 5: WHO CAUSALITY ASSESSMENT OF ADRS

S. No	Type of Adverse Drug Reaction	No of adverse drug reactions (N=40)	Percentage of ADRs (%)
1.	Certain	-	-
2.	Probable / Likely	18	45
3.	Possible	22	55
4.	Unlikely	-	-
5.	Conditional / Unclassified	-	-
6.	Unassessable / Unclassifiable	-	-

TABLE 6: HARTWIG'S SEVERITY ASSESSMENT OF ADRs

S. No	Type of Adverse Drug Reaction	No of adverse drug reactions (N=40)	Percentage of ADRs (%)
1.	Mild	09	22.5
2.	Moderate	28	70
3.	Severe	03	7.5

DISCUSSION: In the present study, 40 out of 92 patients had the ADRs of electrolyte imbalance due to the diuretics usage. A high incidence of 09 ADRs was observed in 13 patients receiving torsemide and spironolactone combination, 07 ADRs was observed in 14 patients receiving furosemide and torsemide combination. No ADRs were reported in one patient receiving spironolactone, and one patient receiving furosemide, torsemide and metalazone.

Diuretics promote the elimination of various electrolytes and this causes hyponatremia, hypokalemia, hypochloremia etc. In the current study, hyponatremia was the ADR observed in 17 patients (42.5%) prescribed with various diuretics. Hypokalemia was the other ADR commonly seen and a total of 12 patients (30%) were reported as hypokalemia. Both hypokalemia and hyponatremia occurred consecutively in 07 patients (17.5%). Studies suggest that thiazide-induced hyponatremia occurs within 1 dayto a median time of one year of drug initiation [9, 10].

This wide variability in the time course for hyponatremia associated with thiazide diuretics is reflective of the varied mechanisms for altered water balance in patients taking thiazides. In the present study, fixed dose combinations of a thiazide and potassium sparing diuretic did not significantly reduce the prevalence of hypokalemia, rather the combination of amiloride-hydrochlorothiazide was associated with an uneven number of cases with hyponatremia. The rationale of the increase in the use of fixed dose combination diuretics over less expensive single agents is questioned.

Loop diuretics affects the potassium concentrations by blocking chloride-coupled sodium re-absorption in the loop of Henlee, and the thiazide diuretics block chloride-coupled sodium re-absorption in the early distal tubule. As a result, both classes of drugs increase Na^+ and Cl^- delivery to the collecting duct, stimulating K^+ secretion and causing chloride depletion. The combination of loop and thiazide diuretics often is used to promote diuresis. This intense diuretic regimen almost invariably causes K^+ depletion and hypokalemia. Both classes of diuretics also increase magnesium excretion, causing depletion of this cat ion. Magnesium depletion itself promotes renal K^+ losses and contributes to K^+ depletion [4]. The study conducted by Rende, *et al.,* also suggested regular monitoring of the serum levels of sodium, potassium, and creatinine, during treatment with loop diuretics, particularly in patients with high risk for electrolyte imbalance or in the presence of liquid loss (*i.e.,* vomiting, diarrhoea, or heavy sweating) [11].

Of the 40 patients with ADRs in the present study, 3 patients developed hyperkalemia as an ADR, who were prescribed with spironolactone (combined with other diuretic) along with Perindopril (ACE inhibitor). The combination of both potassium sparing diuretic and an ACE inhibitor will potentially increase the serum potassium levels (dose dependent), and the situation leads to hyperkalemia. The hypo / hyper effects could be found at any dose and point of diuretic use.

Diuretics were not discontinued in 30 patients (75%) identified with adverse drug reaction of hyponatremia or hypokalemia, as hyponatremia was managed by stopping the concerned medication and if required replacing the lost electrolyte with normal saline or 3% saline solution. Likewise potassium supplements or a potassium sparing diuretic (Spironolactone) were given to manage the hypokalemic effects like arrhythmias, muscle cramps, leg pain, hypotension, etc. In all the patients continued on diuretics, Sodium and potassium correction turned normal on

repeated testing and all the patients recovered from the hyponatremic and hypokalemic effects. The improvements were spontaneous and due to use of antagonists (sodium and potassium supplements) or using a potassium sparing diuretic (spironolactone).

Literature states that ADRs are known to have a significant effect in health care both from a clinical and economic standpoint [12]. The present study suggests that the adverse drug reactions could be minimized, by taking caution while prescribing the medication, by assessing the various abnormalities in laboratory parameters, and predicting the earlier symptoms associated with diuretics therapy. 10 ADRs (25%) were managed by withdrawing diuretic therapy and providing potassium supplementation.

CONCLUSION: The study recommends that the physicians should always pay close attention to the common side effects of diuretic therapy. Evaluation and management of patients with hypokalemia and hypomagnesemia should include a careful review of medication history to determine if a drug capable of causing or aggravating this electrolyte abnormality is present. Therefore, along with monitoring the laboratory parameters, drugs prescribed along with diuretics should be thoroughly verified and the symptoms that may occur should be closely monitored once the diuretic is administered for the patients.

ACKNOWLDGEMENT: The authors express their sincere thanks to the Professor and Head, Department of Cardiology, Sri Ramachandra Medical Center, Chennai, for granting permission to conduct the study in the Intensive Cardiac Care Unit.

DECLARATION OF INTEREST: The authors report no declarations of interest.

REFERENCES:

1. Doshi MS, Patel PP, Shah SP and Dikshit RK: Intensive monitoring of adverse drug reactions in hospitalized patients of two medical units at a tertiary care teaching hospital. J Pharmacol Pharmacother 2012; 3: 308-13.
2. Wilcox CS: Metabolic and adverse effects of diuretics. SeminNephrol 1999; 19: 557-68.
3. Arampatzis S, Funk GC, Leichtle AB, Fiedler GM, Schwarz C and Zimmermann H: Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. BMC Medicine 2013; 11: 83.
4. Sonnenblick M, Friedlander Y and Rosin AJ*:* Diuretic-induced severe hyponatremia*:* Review and analysis *of* 129 reported patients. Chest 1993; 103: 601.
5. Franse LV, Pahor M and Bari MD: Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. Hypertension 2000; 35: 1025-30.
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C and Greenblatt DJ: A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.
7. The use of the WHO–UMC system for standardised case causality assessment. Accessed from: http://www.WHO-UMC.org/graphics/4409.pdf {last accessed on 2014 Feb 12]
8. Hartwig SC, Siegel J and Schneider PJ: Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992; 49: 2229-32.
9. Barber J, McKeever TM, McDowell SE, Clayton JA, Ferner RE and Gordon RD: A systematic review and meta-analysis of thiazide-induced hyponatraemia: time to reconsider electrolyte monitoring regimens after thiazide initiation? Br J Clin Pharmacol 2015; 79: 566 -77.
10. Leung AA, Wright A, Pazo V, Karson A and Bates DW: Risk of thiazide-induced hyponatremia in patients with hypertension. Am J Med 2011; 124: 1064.
11. Rende P, Paletta L, Gallelli G, Raffaele G, Natale V, Brissa N, Costa C, Gratteri S, Giofrè C and Gallelli L: Retrospective evaluation of adverse drug reactions induced by antihypertensive treatment. J Pharmacol Pharmacother 2013; 4(1): 47-50.
12. Sultana J, Cutroneo P and Trifirò G: Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother 2013; 4(1): 73-7.

How to cite this article:
Vikas S, Ramesh M, Rani VN, Thennarasu P and Kannan G: Incidence of diuretics induced adverse drug reactions in an intensive cardiac care unit of a tertiary care teaching hospital. Int J Pharm Sci Res 2017; 8(8): 3557-62.doi: 10.13040/IJPSR.0975-8232.8(8).3557-62.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)