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Effect of Diuretics on the Pharmacologic Action of Warfarin

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Original Research Article

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Abstract: Warfarin is a coumarin derivative that is used to inhibit thromboembolic events. Calcium reabsorption and urinary calcium excretion can be affected by the administration of diuretics, which is an important part of the blood clotting process. The aim of the present study is to explore how diuretics (Furosemide and Hydrochlrothiazide) affect the function of the coagulation cascade in patients using warfarin as an anticoagulant agent through the assessment of Prothrombin time (PT) and international normalized ration (INR) in Queen Alia Heart Institute at the Royal Medical Services (RMS) in Jordan/Amman. A retrospective study will be performed in Queen Alia Heart Institute. Data will be gathered by reviewing the medical records of patients using warfarin (5mg). Of the total 314 patients enrolled in the study, 215 (68.4%) were males. The mean age of the study participants was 67.5 ± 5.6 years. Calcium concentration was significantly reduced in patients taking furosemide with warfarin (group 1) in comparison with those who were taking HCTZ in addition to warfarin (group 2). Furthermore, PT and INR were significantly elevated in patients with group 1 when compared with those in group 2. This study revealed that the combination of hydrochlorothiazide with warfarin decrease the anticoagulant activity of warfarin. Therefore, specialists should be attentive of possible interactions and monitor patients' INR closely.
Keywords: Coagulation, Diuretic, INR, Warfarin.

INTRODUCTION

The most recognized vitamin K-dependent proteins (VKDPs) are the coagulant factors II, VII, IX, and X. They are formed by the liver; transformed into their biologically active forms by the carboxylation of glutamic acid residues, a process necessitating vitamin K as a cofactor. By interfering with this carboxylation process, warfarin has become the central component of anticoagulant therapy [1].

Warfarin, a vitamin K antagonist, is an oral anticoagulant drug frequently used for the inhibition and management of stroke, venous thrombosis, treatment of the thromboembolic complications related to atrial fibrillation and prosthetic heart valves. Moreover, warfarin is approved as an adjunct to lessen the risk of myocardial infarction (MI) and other thromboembolic disorders after a patient's first MI [2]. Vitamin K is crucial for the activation of certain clotting factors (II, VII, IX and X). In this procedure, vitamin K gets oxidized to vitamin K epoxide. There is a mechanism nevertheless, through which the vitamin K epoxide is recycled within the liver back to vitamin K. The enzyme involved is vitamin K epoxide reductase complex 1 (VKORC1) and this is the enzyme that is intensely inhibited by warfarin. Using large doses of exogenous vitamin K will overcome the need to recycle vitamin K epoxide within the liver and will consequently invert the impact of warfarin [3]. Warfarin exhibits its anticoagulation effects thru the intrinsic and extrinsic pathways in the clotting cascade. This happens by preventing the production of vitamin K-dependent clotting factors (II, VII, IX, and X) and the anticoagulant proteins C and S. Warfarin interferes with the synthesis of clotting factors by blocking the vitamin K oxidation-reduction cycle required for the carboxylation of clotting factors. The extrinsic factor system catalyzes both the common pathway and factor IX the intrinsic pathway. Finding of this stimulation of the intrinsic pathway by factor VII in the extrinsic pathway has enhanced reconsideration of the biologic significance of the extrinsic system. The common pathway includes factors X and V and causes thrombin to convert fibrinogen to fibrin. Calcium and platelet phospholipids are substances that have important roles in steps in the coagulation scheme [4]. Warfarin is a racemic mixture of two optically active isomers, the R and S enantiomers. Warfarin is highly water soluble, is promptly absorbed from the gastrointestinal tract, has great bioavailability and attains highest blood levels after 90 min after oral administration. Racemic warfarin has a half-life ($t_{1/2}$) of 35 to 43 h (R-warfarin 44 h, S-warfarin 30 h), circulates bound to plasma proteins, and accumulates in the hepatic tissues where the two

enantiomers are metabolically interconverted by dissimilar pathways [12]. Both Diuretics (loop and thiazide) and warfarin are highly protein-bound to albumin and are fundamental substrates for the CYP2C9 isoenzyme. Competition by several drugs for metabolism through CYP2C9 may reduce the elimination of the drugs from systemic circulation [5]. Adding a drug with highly protein binding capacity may lead to the displacement of other drugs that circulate highly protein-bound. Thus, it is likely that the adding of diuretic may enhance the anticoagulant action of warfarin by competition for metabolism via CYP2C9, with a reduction in the elimination of warfarin, and protein-binding displacement of warfarin from albumin, transiently enhancing anticoagulant activity [13]. Diuretics induced hem concentration with subsequent concentration of clotting factors has been reported to decrease the effects of oral anticoagulants [6].

The aim of this study is to explore how diuretics affect the function of the coagulation cascade in patients using warfarin as an anticoagulant agent through the assessment of Prothrombin time (PT) and international normalized ration (INR).

PATIENTS AND METHOD

This is a retrospective study carried out in Queen Alia Heart Institute at the Royal Medical Services (RMS) in Jordan/Amman. Ethical approval has been obtained from the IRB committees at the JRMS. Patients on warfarin therapy, admitted from January to August, 2017 were followed from the time of admission until discharge. The patients were divided into two groups, patients of group 1 were taking furosemide 80 mg/day plus warfarin 5mg daily for about one year or more, while patients of the second group were taking hydrochlorothiazide (HCTZ) 25 mg daily and warfarin 5mg daily for about one year or more. Results of blood chemistry and complete blood count were accessed through revision of patient's medical profiles. Blood samples were taken from each patient and sent to the hospital lab for measurement of serum calcium concentration, prothrombin time and INR. The result is reported in seconds (prothrombin time).

INR is calculated by the following equation:

[(patient prothrombin time in seconds)/ (mean normal plasma prothrombin time in seconds)]^{ISI}

The mean normal plasma prothrombin time = 12 Sec.

DATA ANALYSIS

Descriptive analyses were reported as were reported as Mean ± standard deviation (SD), and percentage. When comparing continuous variables between the two study groups ANOVA (repeated measure) test was used. The significance level was set at 0.05.

RESULTS

Three hundred and fourteen (314) patients participated in this study. As Table (1)shows, more than two thirds of them (68.4%) were males, and their age ranged between 50 and 75 years. Majority of the patients were unemployed or retired (84%).

The medications of patient's in each group of the two studied groups are summarized in Tables (2).

The details of clinical characteristics of patients are shown in tables 3 and 4.

Table-1: Description of demographic characteristics of patients in the study sample (n=314)

	Group 1 N (%)[1]	Group 2 N (%)[1]
Number of patients	203	111
Age (years): Mean± SD Range	 65.1±5.6 {58-79}	 69.9±4.37 {56-81}
Gender: Male Female	 141 (69) 62 (31)	 74 (35) 37 (65)
Occupation Unemployed Employed Retired	 51 (25.1) 33 (16.2) 119 (58.7)	 35 (31.5) 17 (15.3) 59 (56.2)

1: Percent out of patients in mentioned group.

Table-2: The most common medications used by the study population

Drug	Group 1 (n=203)	Group 2 (n=111)
Frusemide	203	0
Hydrochlorothiazide	0	111
Warfarin	203	111
CaCO3	55	22
Alfacalcidiol	52	13
Nifedipine	88	22
Amlodipine	102	47
Enalapril	103	23
Candesartan	87	59
Bisoprolol	145	22
Atenolol	33	14
Carvedilol	18	32
Hydralazine	45	16
Doxazocin	67	14
Methyldopa	34	18
Subcutaneous insulin	116	44
Aspirin	188	85
Statin	179	71
Sulfonylurea	67	29
Metformin	91	57
Nitrates	153	73
Antihistamine	44	31
Others [1]	56	23

1: Allopurinol, Alendronate Na, Gemfibrizoil, Multi vitamins, Tamsolucin, PPI, Proton Pump Inhibitor

Table-3: Blood chemistry baseline characteristics for the participants

Test	**Group 1 (n=203)**	**Group 2 (n=111)**
BUN (mg/dl) Mean± SD	14.5±5.2	12±4.5
SCr (mg/dL) Mean± SD	0.93±0.01	1.0±.031
Na (mEq/L) Mean± SD	138±20.9	134±22.2
K (mEq/L) Mean± SD	4.7±1.23	4.3±1.18
Ca (mg/dl) Mean± SD	8.01±0.26	10.32±0.39
PO4 (mg/dl) Mean± SD	3.9±0.8	3.52±0.71

Table-4: Complete blood count for the participants in the study

Test	Group 1 (n=203)	Group 2 (n=111)
Hemoglobin (g/dL) Mean± SD	12.8±3.7	11.95±3.98
Hematocrit % Mean± SD	38.1±7.02	37.3±5.12
MCV (fL) Mean± SD	89±7.6	89.3±6.19
RBCs (10^6/uL) Mean± SD	4.8±0.73	4.45±0.68
Platelets (10^3/uL) Mean± SD	215±45.9	221±65.4
WBCs (10^3/uL) Mean± SD	6.01±1.7	6.6±1.53

MCV, Mean Corpuscular Volume; RBC, Red Blood Cell Count; WBC ; White Blood Cell Count.

Effect on serum calcium level

The results of the study revealed that there was a significant reduction (P<0.01) in calcium concentration in patients taking furosemide with warfarin (group 1) in comparison to those who were taking HCTZ in addition to warfarin (group 2) as shown in table (5).

Table -5: Means of serum calcium level in mg. /dl of the two groups and the mean difference between the two groups

Groups	Serum calcium(mg/dl)	Mean Difference
Group 1	8.01 ± 0.26	**
Group 2	10.32 ±0.39	+2.38**

Data are expressed as mean±SEM

*p-value obtained by ANOVA test, statistically significant if p value<0.05

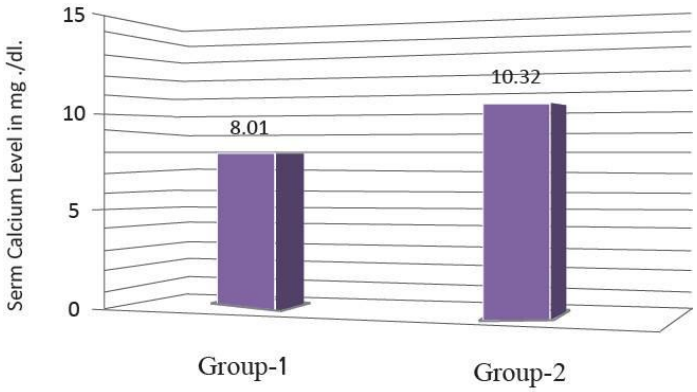

Fig-1: Comparative effect of HCTZ and furosemide on serum calcium level in mg/dl

Effect on prothrombin time

The results showed that there was a statistically significant difference (P<0.05) in prothrombin time between the group of patients who were administered furosemide plus warfarin (group1) and the group of patients who were administered HTZ plus warfarin as shown in table (6).Table (6). Means of prothrombin time in seconds of the two groups and the mean Difference between the two groups.

Groups	PT (seconds)	Mean difference
Group 1	23.2 ± 0.51	+1.36*
Group 2	20.02 ±0.31	- 1.36*

Data are expressed as mean±SEM

*p-value obtained by ANOVA test, statistically significant if p value<0.05

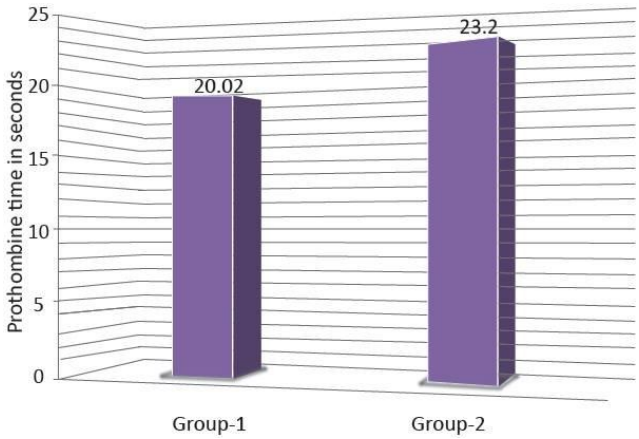

Fig-2: Comparative effect of hydrochlorothiazide and furosemide on prothrombin time

Effect on INR: There was a statistically significant difference (P<0.05) in INR between the group of patients who were receiving furosemide plus warfarin and when compared with those who were receiving HCTZ plus warfarin as shown in table (7).

Table (7). Means of prothrombin time in seconds of the two groups and the mean difference between the two groups.

Groups	INR	Mean difference
Group 1	2.51 ± 0.13	+0.51*
Group 2	2.07 ±0.069	- 0.51*

Data are expressed as mean±SEM

*p-value obtained by ANOVA test, statistically significant if p value<0.05

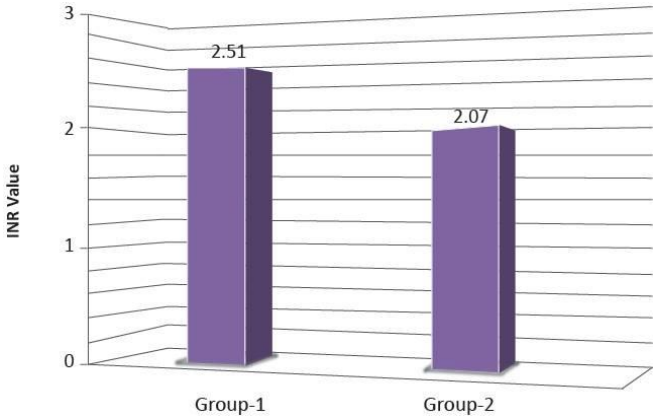

Fig-3: Comparative effect of hydrochlorothiazide and furosemide on INR

DISCUSSION

The results of this study showed that patients taking furosemide with warfarin exhibits a significant reduction in blood calcium concentration in respect with those patients who were taking HCTZ with warfarin and this is in fact may be elucidated as a result of the inhibition NaCl transport at the NKCC2 transporter in the ascending loop of Henle and accordingly the driving force for Ca^{++} reabsorption. They consequently increase Ca^{++} excretion [7], whereas thiazide diuretics which act by increasing proximal tubular calcium reabsorption as a secondary consequence of direct action of thiazides on the distal tubule [8]. Even though the mean INR value in the two study groups was within the desired limit (2-3), but its mean value was in the lower wanted therapeutic limit (2.07) in group 2. The mean INR value was in the middle required therapeutic range (2.51) in group 1 and such increase in INR value was statistically significant in comparison with patients in group 2. Moreover, there was a statistically significant reduction in prothrombine time in patient in group 2 with warfarin when compared with those in group 1.

These results can be explained by the action of thiazide diuretics on serum calcium concentration as thiazide diuretics elevate serum calcium concentration, this result in enhancing activation of clotting factor X which will lead to a reduction in the anticoagulant activity of warfarin which results in a decrease in prothrombin time and INR [9]. Additionally, diuretics may reduce the response to warfarin by decreasing the plasma volume, with a consequent rise in clotting factor activity [10]**.** Conversely, furosemide reduce calcium concentration which will enhance the activation of clotting factor X, but this effect is counterbalanced by the action of diuretics in decreasing plasma volume with a following rise in clotting factor activity, so furosemide may not modify the response to warfarin [11].

CONCLUSIONS

Warfarin is well-known for its inconstant dose–response correlation, narrow therapeutic window, possible bleeding risk and the probability for several drug and dietary interactions. Thus, checking the international normalized ratio (INR) is critical for keeping the drug within its narrow therapeutic index of 2.0–3.0. In this study, warfarin – diuretics interactions were obvious. Health care specialists should be attentive to possible drug interaction while prescribing diuretics in patient on warfarin. Patients should also be counseled about drug interactions, sign and symptoms of warfarin related bleeding complication.

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