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Case Report

Case Presentation of a 45 Years Old Woman with Hypoglycemia and Bleeding

Soha Namazi*, Gholamreza Rozitalab

Faculty of Pharmacy, Shiraz University of Medical Science, Shiraz, Iran

Abstract

A patient was admitted to the hospital because of epistaxis, ecchymoses and gum bleeding with INR of 5.5. This patient had a known case of diabetes mellitus type II, 5 years ago. The last dose of glibenclamide for managing signs and symptoms of diabetes mellitus was 20 mg/day. Her medical history also showed that last month she was diagnosed with atrial fibrillation with normal left ventricular ejection fraction (LVEF> 45%) and was placed on warfarin (5 mg) and propranolol (80 mg) daily, which resulted in resolution of atrial fibrilation, a pulse rate of 80 bps and INR of 3 (target INR=2-3). An objective causality assessment indicated the increased effect of warfarin and as a result bleeding could best be explained by drug-drug interaction because there are no other factors such as pathological evidences (e.g. thyroid disease, hepatic disorders) to prove it otherwise. This case is the third report of drug interaction between warfarin and glibenclamide, therefore, this is an interesting and educational case.

In view of our experience in the present case, it should be stressed that close monitoring of coagulation capacity is necessary in co-administration of warfarin and other drugs which can affect pharmacokinetic and pharmacodynamic of warfarin.

Keywords: Drug interation; Glibenclamide; Warfarin.
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1. Background

A 45 year-old female was admitted to the hospital because of epistaxis, ecchymoses and gum bleeding. A review of her prior history revealed that she was diagnosed with diabetes mellitus (DM) type-II, 5 years ago. The signs and symptoms of DM were fairly controlled with glibenclamide 15 mg daily. Findings during her last visit were: fasting plasma glucose (FPG) 205 mg/dl and glycosylated hemoglobin (HbA_{1C}) 8.5%. Her medical history also showed that last month she was diagnosed with atrial fibrillation (AF) with normal left ventricular ejection fraction (LVEF> 45%) and was placed on warfarin 5 mg and propranolol 80 mg daily, which resulted in resolution of AF, a pulse rate of 80 bps and INR of 3 (target INR 2-3).

A week prior to her admission, she had a visit to her family physician, complaining of symptoms of hyperglycemia (e.g. polyurea, polydipsia, etc). At that time, her FPG was

*Corresponding author: Soha Namazi, Department of Pharmacotherapy, Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran, P.O. Box 71345-1583.
Tel (+98) 711-2424128, Fax (+98) 711-2426070
E-mail: sohanamazi@yahoo.com

reported at 225 mg/dl. Her physician recommended an increase in glibenclamide dose to 20 mg/day plus a more sensible diet and exercise. A week later, since the glibenclamide dose increase, she came to the ER with signs of warfarin overdose (epistaxis, ecchymoses, and gum bleeding) and the results of her lab work showed: INR of 5.5. At this time, warfarin was discontinued, and she received a dose of 0.5 mg vitamin K_1 (i.v.). She was under a close watch until her INR was down to an acceptable level. Then, her warfarin was re-started with a dose of 2.5 mg daily and was increased until INR value was controlled.

At the fifth day of the warfarin dose adjustment, the patient showed signs of confusion, lethargy and loss of consciousness. At that time, her plasma glucose level was reported at 42 mg/dl. Measures were taken to treat hypoglycemia (using 50% dextrose in water and discontinuing glibenclamide) and a complete evaluation of the patient was warranted. No specific finding was helpful in determining the cause of hypoglycemia; with the exception of last week's glibenclamide dose increase. To avoid hyperglycemia, the glibenclamide dose was re-started at 10 mg daily and tapered up as necessary. Seven days later, the cycle repeated itself. The patient showed symptoms of warfarin overdose with INR of 5.2, and the warfarin was again discontinued.

2. Discussion

The problem inherent in any anticoagulant is the risk of hemorrhage. The annual incidence of major hemorrhage (usually defined as intracranial hemorrhage or hemorrhage causing death or necessitating transfusion or hospitalization) has ranged between 1.2 and 7.0 episodes per 100 patients in different cohort studies [1], whereas in clinical trials with selected patient populations, it has ranged between 0.5 and 4.2 per 100 patients [2]. Minor bleeding episodes are those that have no costs or consequences; the annual incidence of such bleeding is 2-24 episodes per 100 patients. The risk of hemorrhage is closely related to the intensity of anticoagulation. With an increasing duration of treatment, the risk of major hemorrhage increases cumulatively [2]. Although this issue is subject to debate, the risk of bleeding may be higher during the first month of anticoagulant therapy and then decrease gradually, owing to the fact that the prothrombin time fluctuates more, initially [1]. Other predictors of hemorrhage include poor control of the degree of anticoagulation, peripheral vascular disease, and in some studies, old age [3]. Additional hurdles to overcome in achieving satisfactory anticoagulation are the multitude of interaction between vitamin K antagonists and other drugs or foods (such as: spinach, avocado), problems with monitoring the degree of anticoagulation, and lack of knowledge about how to adjust the dose [4]. The list of drugs (up to 80) that interact with vitamin K antagonist is constantly expanding (Table 1) [1], and every change in the patient's medication should be considered. The major known sites of interaction are firstly the plasma proteins, where warfarin is approximately 99% bound to serum albumin, but this interaction can not be significant in clinical setting [5, 6], and secondly the hepatic CYP450 system [7].

Warfarin is a racemic mixture containing equal parts of the enantiomers R(+) warfarin and S(-) warfarin. The S-isomer is 2.7-3.8 times more potent as an anticoagulant than the R-isomer [8]. These enantiomers are metabolized differently by CYP450 system enzyme, where S(-) warfarin broken down by the CYP2C9 and R-warfarin is metabolized by CYP1A2, CYP3A4, and CYP2C19 [9]. Previous studies, indicated that population differences in the frequencies of known variant CYP2C9, CYP2C19 alleles account in part for the variability observed in *in vivo* warfarin activity in different populations [10, 11].

Glibenclamide is one of the drugs that affect the anticoagulation effect of warfarin [1], but only 2 cases have been reported [12]. Glibenclamide inhibited CYP2C9–catalyzed S-warfarin 7-hydroxylation most significantly, with a k_i of 2.4 μM. Although this effect is weaker than that of sulfaprazole (k_i<1 μM), it is more potent than any other CYP2C9 inhibitor, including fluconazole (k_i= 8 μM). This drug inhibited approximately 7-37% of the *in vivo* clearance of warfarin, a CYP2C9 substrate. Other CYP450 isoenzymes (CYP 1A2, 2C8, 2C19, 2E1 and 2D6) are not affected by glibenclamide, however CYP3A4 is inhibited weakly [9]. All sulfonylureas are highly protein bound (90-100%), mainly to albumin, however, binding characteristics vary between individual sulfonylureas. Glibenclamide binds to human serum albumin by nonionic force in contrast with first-generation sulfonylureas [13].

Thus ionic drugs such as warfarin and salicylate do not displace glibenclamide from albumin as they displace first generation sulfonylureas. Other studies also support this finding [14]. As mentioned previously, protein binding displacement of warfarin is usually an unlikely mechanism for drug interaction [15]. The unbound concentration usually returns to the original level after several days of treatment by redistribution to peripheral tissues and compensatory activation of metabolism [16], but in this patient the elimination of unbound warfarin would have been significantly delayed because of reduced intrinsic clearance (CYP2C9) by metabolic inhibition. Therefore, the inhibition of CYP2C9 seems to explain the observed drug interaction of glibenclamide with warfarin.

There are many reasons for the appearance of the manifestations of hypoglycemia, such as drugs, diet, illnesses, and physical activity [17]. In patients with diabetes type II, the use of sulfonylureas, which are the first-line drug therapy, seems to be the main reason [8, 13]. Among sulfonylureas, those with longer half life are usually associated with more incidence of hypoglycemia due to their prolonged effect and also more drug interactions with other agents [18]. Glibenclamide has a great tendency to cause hypoglycemia [11]. Duration of therapy, concomitant use of insulin, drugs that potentiate effect of sulfonylureas, and concomitant use of b-adrenorecptor antagonist are predictive of the risk of developing hypoglycemia [19-21].

Drug interactions happen by two mechanisms. Drugs that have an indirect effect on sulfonylureas by changing the utilization of glucose, or by having a hypoglycemic effect. Drugs that have a direct effect by changing sulfonylureas pharmaco-kinetic (e.g. absorption, metabolism, excretion and protein binding) [22].

The effect of anticoagulants on sulfonylurea has been discussed in some studies [12]. Previous studies have shown that dicumarol (a close relative of warfarin) increases the half life of tolbutamide and chlorpropamide by 3 to 4 folds, perhaps by affecting their hepatic metabolism [8, 21]. Second generation sulfonylureas such as glibenclamide, in general, have less potential for drug interaction. Studies show that highly protein bound drugs such as warfarin does not significantly affect glibenclamide displacement [14].

Since there are no solid reports on the adverse effects of warfarin on the metabolism and protein binding of glibenclamide [12], we can conclude that in this patient, it is unlikely that warfarin could have caused hypoglycemia. Because even if warfarin was the causative agent, after discontinuation of warfarin we would expect to see evidence of decreased glibenclamide effect and as a result signs of hyperglycemia, because either more glibenclamide molecule would be protein bound and unavailable or metabolized by the liver. However, this mechanism may explain the first observed hyperglycemia at starting warfarin dose. Although there are no reports

of hypoglycemia/hyperglycemia by interaction between warfarin and glibenclamide [12], it is highly recommended that because of different individual responses to this combination whenever a dose adjustment is needed, patient be closely observed and monitored for signs and symptoms of hypoglycemia/hyperglycemia.

Another drug that can exacerbate hypo/hyperglycemia and hypoprothrombinemia in this patient is propranolol [21]. This drug can affect the patient's blood glucose levels in two different ways: 1) By masking the hypoglycemic symptoms: tachycardia, palpitation, sweating, and tremors, (such as in this case). 2) By decreasing insulin secretion and therefore increasing blood glucose (it is worth noting: in acute propranolol overdose, hypoglycemia is often observed) [23].

In this patient, considering the dosage and duration of propranolol usage, it could be blamed for the incidence of hypoglycemia, but it could explain initial hyperglycemia.

Studies show that the effect of warfarin is augmented by propranolol and the exact mechanism by which this effect is exerted is not fully understood [24, 25]. A probable mechanism is that propranolol displaces warfarin on α-1 acid glycoprotein, however, the clinical importance of it is yet to be established [26]. On the other hand, warfarin has a low extraction ratio metabolism, therefore, propranolol can not be affected by its hepatic uptake and metabolism [27].

In general, β-blockers are safe agents to use and seldom we observe drug interactions when used with other agents, but since variation in pharmacokinetic and pharmacodynamic responses of different individuals to β-blockers exists [26, 28], it would be logical to use an alternative drug in cases where there is a drug interaction possibility, or at least a less protein bound and more β-1 selective blocker (e.g. atenolol, metoprolol) should be utilized. Therefore, to control the arrhythmia (AF) in this patient, considering the fact that she does not suffer from heart failure or heart block, verapamil or diltiazem could be used instead of propranolol. Another advantage would also be a favorable effect on her blood glucose level.

3. Conclusions

We discussed a patient case and tried to

Table1. Major drug interactions with warfarin [4]*.

Anticoagulant response increased	Anticoagulant response decreased
Acetaminophen	Antithyroid drugs
Amiodarone	Barbiturates
Androgens (17-alkyl)	Carbamazepine
Cimetidine	Cholestryramine
Clofibrate	Dichloralphenazone
Disulfiram	Glutethimide
Erythromycin	Sucralfate
Fluconazole	
Fluoxetine	
Glucagon	
Metronidazole	
Oxyphenbutazone	
Phenylbutazone	
Salicylates (high dose)	
Sulfinpyrazone	
Tamoxifen	
Thyroid hormone	
Trimethoprime-sulfamethoxazole	

*An extensive list of drug interactions can be found in Schulman [1].

explain the mechanisms by which complications have occurred. The increased effect of warfarin and as a result bleeding could best be explained by drug-drug interaction because there are no other factors such as pathological evidences (e.g. thyroid disease, hepatic disorders) to prove it otherwise. It seems that among predisposing factors the drug interaction between warfarin, glibenclamide and propranolol have clinical importance and to correct this patient's situation and to prevent the roller-coaster complications, the following is recommended: propranolol is highly protein bound (90%) and as discussed earlier, it can possibly affect the therapeutic outcome of warfarin and also its undesired effect on glycemic control [21] makes it a candidate for discontinuation to be replaced with either verapamil or diltiazem. This could positively affect clinical outcomes.

Considering the patient's FPG, HbAc1, and diabetic symptoms, and the fact that this patient has experienced hyperglycemia in the past week, it is highly possible to see secondary failure with sulfonylureas. Some authors believed that if blood glucose level is not controlled with glibenclamide (10 mg/day), a dose increase will be of no value [8], therefore, it seems logical to either change the sulfonylurea or combine it with another agent. Because the dose of glibenclamide is greater than a half of the maximum dose, thus another agent should be added [22].

Nonsulfonylurea alternative agents available in Iranian market are metformin, rosiglitazone and acarbose. In addition to the price and availability, metformin is currently normally the first adjunctive drug to be added to sulfonylurea therapy [29, 30]. Since a dose increase of glibenclamide can more inhibit the warfarin metabolism [9], and complicate the case, a lower dose of glibenclamide (e.g. 10 mg/day) plus metformin is recommended with cautiously tapering up the metformin dose to achieve glycemic control. There is no evidence of interaction between warfarin and metformin [12]. The use of insulin is not recommended at this time because of the possibility of risk of bleeding at the injection site. If FPG and HbA_{1C} were not controlled or hemorrhagic events reoccurred, at this time another regimen should be applied such as: metformin + thiasolidindiones, metformin + insulin/thiasolidindiones and insulin alone [31].

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