

Warfarin interactions: A letter to editor

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ARTICLE INFO	ABSTRACT
<p><i>Article type:</i> Letter to the editor</p> <hr/> <p><i>Article History:</i> Received: 7-Nov-2019 Accepted: 15-Dec-2019</p> <hr/> <p><i>Key words:</i> Anticoagulants, Drug interaction, Warfarin</p>	<p>Today, with the advances in the treatment of cardiovascular patients such as intravascular stents, cardiac valves and intraventricular pacing and heart transplantation, many patients require the use of anticoagulants such as warfarin, sprain, Plavix, osvix, Ticlopidine and other drugs. Drugs that cause warfarin toxicity can also disrupt patients' hemodynamic conditions and can be dangerous in older people with underlying diseases. This review study examines some of the most common drug interactions with warfarin. Considering the increasing use of herbal medicine by patients, the importance of educating patients on warfarin is crucial, as many of these drug interactions are dangerous and life-threatening. Due to widespread drug interactions with warfarin and comprehensive use of non-prescription drugs in our country, accurate education and training of warfarin users is of paramount importance.</p>
<p>► Please cite this paper as: Sadrzadeh SM, Vafadar Moradi E, Mousavi SM, Rezvani Kakhki B, Rahmani Sh. Warfarin interactions: a letter to editor Journal of Patient Safety and Quality Improvement. 2019; 7(4): 181-183. Doi: 10.22038/psj.2019.44292.1250</p>	

Introduction and the importance of the subject

Today, with the advances in the treatment of cardiovascular patients such as intravascular stents, cardiac valves and intraventricular pacing and heart transplantation, many patients require the use of anticoagulants such as warfarin, sprain, Plavix, osvix, Ticlopidine and other drugs (1). For over 50 years, warfarin has been one of the most effective oral coumarin anticoagulants. Warfarin reduces the synthesis of vitamin K-dependent factors (2). It is usually prescribed with a large number of different medications in patients, which may have different interactions.

Pharmacokinetic interaction refers to the effect of one substance on the absorption, distribution, metabolism, and elimination of another substance in the body (3,4).

Pharmacodynamic interactions are those which change one substance's effects to another's (1). These include antagonistic and synergistic or additive interactions (2).

In antagonistic interactions, a drug with an agonist effect on a particular receptor type interacts with its receptor antagonists (5). In additive or synergistic interactions, co-administration of two drugs with similar pharmacological effects may increase their efficacy (1).

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Drug interactions with warfarin alter the serum levels of this drug, increasing or decreasing its efficacy, and this is especially important in patients with artificial valves who need to maintain coagulation markers within a specific therapeutic range (3). Drugs that cause warfarin toxicity can also disrupt patients' hemodynamic conditions and can be dangerous in older people with underlying diseases. This review study examines some of the most common drug interactions with warfarin.

Evidences

In a study in South Africa, only 17% of patients with warfarin toxicity had complications from drug interactions (1).

In a study in Egypt in 2016, authors revealed that patients with warfarin toxicity and an INR above 4 were often more likely to take more than one interacting drugs with warfarin (2).

Various studies have shown that concomitant use of warfarin with some drugs increases the anticoagulant effects of this drug and increases the risk of bleeding disorders. For example, allopurinol, amiodarone, anabolic steroids, androgens, oral anti-diabetic agents, salicylates, cephalosporins, chloramphenicol, cimetidine, clofibrate, danazol, dextran, Ibuprofen, Mefenamic Acid, Methimazole, Metronidazole, Phenytoin (first increasing and then decreasing anticoagulant effect), propylthiouracil, quinidine, sulfonamides and thyroid hormones (3-5).

On the other hand, concomitant use of certain drugs such as antacids, ascorbic acid (in large quantities), barbiturates, carbamazepine, cholestyramine, and oral antihypertensive drugs (may increase or decrease the effect of the Warfarin), estrogens, griseofulvin, rifampin and vitamins with Warfarin may reduce the anticoagulant effect of this drug (3,4). A study in 2014 showed that, the most important antibiotics that were associated with an increased risk of bleeding in these patients were azithromycin, cotrimoxazole, ciprofloxacin, levofloxacin, and clarithromycin (5).

One of the most commonly used antibiotics is metronidazole, nowadays and due to its mechanism of action the possibility of drug interference is predictable. However, many cases of interactions between metronidazole

and warfarin have not been reported so far. In a 2014 case study of concomitant use of metronidazole and warfarin caused intracranial hemorrhage (2).

It seems that concurrent use of several antibiotics appears to increase the risk of warfarin toxicity. According to our search, there were not many recent articles on the interactions of antacids and H2 antagonists with warfarin, and previous papers confirmed the possible effect of these drugs on warfarin clearance (1).

Antidepressants, selective serotonin reuptake inhibitors (SSRI), and sedatives are important drugs that are widely and arbitrarily used by patients today. A study showed that drugs such as citalopram and sertraline interacted less with warfarin, but fluoxetine and fluvoxamine increased the chance of warfarin toxicity (2). Another large US observational study of 52,119 patients confirmed that selective serotonin reuptake inhibitors that inhibit CYP2C9 increase the risk of bleeding in warfarin-administered patients (3).

According to our hospital emergency surveys, many patients do not know enough about the potential role of drug interactions in increase or decrease anticoagulant effects of warfarin. A 2008 study in Lebanon showed that patients' knowledge of the dose required for daily intake, drug interactions, and the therapeutic range of INR was negligible. In this study, patients were trained by a pharmacologist about the effects, interactions, and symptoms of warfarin risk (1).

Considering the increasing use of herbal medicine by patients, the importance of educating patients on warfarin is crucial, as many of these drug interactions are dangerous and life-threatening.

Conclusion

Due to widespread drug interactions with warfarin and comprehensive use of non-prescription drugs in our country, accurate education and training of warfarin users is of paramount importance.

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