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Drug Interactions and Risk of Bleeding among Patients with Atrial Fibrillation (AF) Discharged with Warfarin

التداخلات الدوائية وخطر الأصابة بالنزيف عند مرضى (atrial fibrillation) الذين يستخدمون دواء warfarin

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Abstract

The objective of this study was to examine and evaluate the frequency of bleeding and serious drug interactions among patients with atrial fibrillation (AF) treated with oral anticoagulant [Warfarin]. A random sample of 59 patients from Al-Watni government hospital in Nablus with a principal or secondary discharge diagnosis of AF was identified. All drug and clinical data were abstracted from the patient's files. We excluded patients who were less than 65 years of age, or left the hospital against medical advice, and those whose AF was transient or could not be confirmed. Of the original 59 AF patients, 19 were cliagnosed who were discharged on Warfarin. The mean age for these patients was 71.7 years. Among the patients discharged on Warfarin, 94.7 % had one or more drug – drug interactions that could lead to increase risk of bleeding. Many patients discharged on Warfarin were having multiple interacting drugs. Patient counseling and follow-up monitoring are essential and should be carried out to minimize the risk of bleeding and other complications.

Key Words: atrial fibrillation, warfarin, drug interactions, bleeding, stroke, aspirin, International Normalized Ratio (INR), hemostasis.

ملخص

الاهداف: اختبار وتقييم احتمالية الأصابة بالنزيف والتداخلات الدوائية عند المرضى المصابين ب atrial fibrillation ويستخدمون المميعات الدموية (warfarin). **طريقة البحث**: عينة عشوائية مكونة من ٥٩ مريضا" تم تشخيصهم ب atrial fibrillation في المستشفى الوطني الحكومي – نابلس. وقد تم استخلاص جميع الأدوية والمعلومات السريرية من ملفات المرضى. كما تم استثناء المرضى الذين تقل اعمارهم عن ٦٥ سنة، أو الذين خرجوا من المستشفى خلافا" لنصيحة الطبيب، أو اولئك الذين كانو يعانون من حالة atrial fibrillation مؤقتة أو لم يتم تأكيدها. **النتائج**: لقد توصلت الدراسة إلى أنه من أصل ٥٩ مريضا" مصاباً atrial fibrillation، هناك ١٩ مريضا" تم اخراجهم من المستشفى بوصفة warfarin. وكان معدل أعمار هؤلاء المرضى ٧١,٧ سنة. ومن بين المرضى الذين تم صرف دواء warfarin لهم كان ٩٤,٧% لديهم تداخلات دوائية (واحد أو أكثر) من هذه التداهلات قد تؤدي الى خطر النزيف. **المناقشة والاستنتاج**: عدد كبير من المرضى الذين تم صرف دواء warfarin لهم، كان لديهم الكثير من التداخلات الدوائية. وارشاد المرضى ومتابعة تأثير الدواء عليهم ضروري في هذه الحالة، وذلك للتقليل من احتمالية الأصابة بالنزيف والمضاعفات الأخرى.

Introduction

Atrial fibrillation (AF) is a serious type of cardiac arrhythmia that is commonly seen among elderly patients. It is usually associated with increased morbidity and mortality rate due to an increase in the risk of thromboembolic stroke [(1)] . Warfarin, an oral anti-coagulant (OAC) drug, is highly effective in preventing the thromboembolic conditions associated with AF. The mechanism of action for warfarin includes prevention of intra-hepatic metabolism of vitamin K epoxides and an induction of vitamin K deficiency [(2)].

Recent studies of antithrombotic therapy in atrial fibrillation showed that adjusted doses of warfarin reduced the risk of stroke by about 60%, with absolute risk reductions of 3% a year for primary prevention and 8% a year for secondary prevention. In contrast, low dose aspirin reduced the risk of stroke by about 20%, with absolute risk reductions of 1.5% a year for primary prevention and 2.5% a year for secondary prevention [3, 4]. This indicates that warfarin is superior to low dose of aspirin in reducing the risk of thromboembolic stroke. Unfortunately, warfarin has multiple drug and food interactions that limit its use [5]. The most common contraindications for OACs include evidence of active bleeding, uncontrolled severe hypertension, recent brain, eye or spinal cord surgery or injury, inability for INR monitoring, and patient non-compliance [6]. The OACs have multiple interactions with other drugs and some food components. The most common agents associated with enhanced anticoagulant effect are allopurinol, common analgesics, antiarrhythmics, antidepressants, antidiabetics, antimalarials, antiplatelets, anxiolytics, disulfiram, levothyroxine, lipid regulating agents, testosterone, and alcohol. Oral contraceptives, raloxifene, retinoids, rowachol, and vitamin K have the opposite, reducing effect on the anticoagulation of warfarin. The purpose of this study was to examine the prevalence, nature and frequency of warfarin drug interactions that would increase the risk of bleeding among patients with AF.

Material and Method

The medical files of 59 patients diagnosed with AF were reviewed and investigated. Access to the medical files were made possible after permission from hospital administration and based on an educational agreement between An-Najah University and the Ministry of Health. The medical files reviewed were those obtained from the intensive care unit (ICU) of Al-Watni medical hospital in Nablus /Palestine between Jan. 2004 and April. 2005. Our focus in this study was on patients older than 65 years of age, diagnosed with AF and prescribed warfarin on discharge. Ninteen (19) out of the 59 diagnosed patients fit these criteria. To investigate the risk of drug interactions among patients with AF and prescribed warfarin, all other co-prescribed drugs were obtained from the medical files and classified as those that could increase international normalized ratio (INR) like antibiotics, those that could inhibit haemeostasis like aspirin or both. This classification was based on information obtained from *Drug Interaction: Facts and Comparison* [7]. All data obtained, including those relevant to risk of drug interaction were entered into SPSS (Statistical Package for Social Sciences) and analyzed. The statistical analysis included frequencies and cross tabulation shown in results.

Results

Nineteen (19) out of the 59 patients diagnosed with AF were discharged with a prescription containing warfarin. The 19 patients had an average age of 71.7 years. The majority were males (84%). Most of the patients in this group had other multiple co-morbid conditions: 26.3% had a history of coronary artery disease (CAD), 42.1% have a history of diabetes mellitus (DM), and 42.1% had either an old or recent stroke. It is noteworthy that these conditions, in the presence of AF and advanced age, increase the risk of thromboembolic stroke.

Analysis of the medications prescribed for the patients at the discharge charts showed that 18/19 (94.7%) of the patients discharged with warfarin were co-prescribed at least one medications that could interact with warfarin. Fourteen patients (14/19; 73.7%) were co-prescribed medication that prolong the INR, twelve patients (12/19; 63%) were co-prescribed medications that inhibit haemostasis, and nine patients (9/19; 47.3%) were co-prescribed both types of medications, i.e. medications that prolong INR or inhibits hemostasis. The interacting medications that increases INR were mainly H2-receptor antagonists followed by antibiotics, statins and amiodarone. The interacting medications that inhibit hemostasis were mainly low dose aspirin and low molecular weight heparin. Warfarin is an example of drugs that inhibit homeostasis and increase INR. Investigating the extent of polypharmacy among the patients having interactions with warfarin showed that approximately 95% of the patients had at least one interacting drug with warfarin (Table 1).

Table (1): Extent of polypharmacy and interacting drugs among patients discharged with warfarin.

Number of drugs interacting with warfarin and co-prescribed to the patient.	**Percentage of patients (n = 19 patients) having the assigned number of drug interactions**
0.0	5.3
1	26.3
2	47.4
3	10.5
4	5.3
6	5.3
Total	**100**

Discussion

A total of fifty nine (59) patients diagnosed with AF were initially considered for this study. All the patients were ≥ 65 years old. Only 19/59 (32.2%) patients were discharged on warfarin. Those 19 patients were included in the analysis and the study. Although there may be unidentified reasons that have excluded the use of warfarin among the studied patients, this is considered a low utilization rate based on the assumption that all patients with AF should receive warfarin unless otherwise contraindicated. Under utilization of warfarin may be due to fear of increasing risk of bleeding which is known to increase among patients having chronic diseases or polypharmacy. Among the 19 patients discharged on warfarin, approximately 95% had at least one medication that could interact with warfarin and thus increase the risk of bleeding. The interacting drugs could lead to an increase in INR or inhibit hemostasis or both. Among the 19 patients discharged with warfarin, the total number of interacting medications that may elevate INR was 24, while the total number of interacting medications that could directly inhibit hemostasis was 15. The most frequent interacting medications prescribed concomitantly with warfarin and may elevate the level of INR were the histamine receptor blockers (H_2B), followed by the antibiotics. Both classes of drugs have been shown to inhibit warfarin metabolism, thus potentiating the hypoprothrombotic effect of warfarin[8]. Co-prescribing warfarin and H2-receptor blockers reflect lack of awareness among physicians about certain types of drug interactions. Other studies needs documentation have found that antibiotics were the most interacting medications co-prescribed with warfarin. In this study, 10.5% of patients received concomitant therapy with warfarin and the antiarrhythmic agent amiodarone. The interaction between these two agents is well documented and occurs in virtually all patients receiving this combination. Amiodarone inhibits the metabolism of the R- and S-enantiomers of warfarin. The interaction may be observed as early as 3–4 days after starting amiodarone or may be delayed up to 3 weeks. Following discontinuation of amiodarone, the potentiating effect on warfarin may persist for weeks to months. Among the 19 patients discharged with warfarin, there were 15 medications, mostly low dose aspirin, that were co-prescribed with warfarin and directly inhibit hemostasis. Aspirin irreversibly acetylates cyclooxygenase enzyme in platelets, thus inhibiting platelet function for up to 7–10 days. None of patients were prescribed antiplatelet agents other than aspirin. Three patients were prescribed anticoagulant agents either unfractionated heparin (UFH), or low molecular weight heparin together with warfarin. In conclusion, chronic atrial fibrillation appears to be under treated. Patients with AF who were taking warfarin were widely prescribed drugs with potential interactions that could place them at increased risk for bleeding. Many patients received multiple interacting drugs. In this study, the majority of these agents were histamine 2 receptor blockers, antibiotics, and aspirin. Patient counseling and follow-up monitoring are essential since the impact of these interactions may be delayed until after hospital discharge. Additional studies are needed to examine the impact of these potential interactions on long-term patient outcomes.

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