ROLE OF CLINICAL PHARMACIST IN ANTICOAGULATION MANAGEMENT

KLINIKINIO VAISTININKO VAIDMUO GYDANT ANTIKOAGULIANTAIS

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ABSTRACT

Key words: Warfarin, drug-drug interactions, anti coagulation, dose.

Warfarin is the most widely prescribed oral anticoagulant. Because of substantial interpatient differences in sensitivity to warfarin, numerous variables that can alter the response to therapy with time, and the potential risk for major hemorrhage, a systematic approach to therapeutic drug monitoring must be carried out for every patient with anticoagulant therapy.

The purpose. To identify most frequent existent possible warfarin interactions in the hospital drug prescribing, analyze the effects of interactions on the warfarin dose for cardiological elderly patients.

Materials and methods. In this study patients (age >65) with indications for warfarin therapy from cardiological department of the hospital were included at the time from May 2008 to September 2008.

Results. A total of 100 patients (60 male, 40 female) met the study inclusion criteria. The mean age was 69 ± 3 years. Patients received warfarin treatment for the following indications: atrial fibrillation (n = 43), other rhythm disorders (n = 29), cardiomyopathy (n = 21) prosthetic valve (n = 7).

Concomitant other drugs were analyzed which are known either to prolong the prothrombin time or international normalized ratio (INR) or interact with warfarin such as amiodarone (25 %), statins (13 %), anti-inflammatory drugs (aspirin (4 %)), proton pump inhibitor (omeprazole (4 %))

In this study we found inverse correlation between starting dose of warfarin and maintenance dose of amiodarone ($r^2 = 0.94$, $p < 0.005$). When we calculated the dose of anticoagulant for these patients, it seemed to be decreased for 32% mean maximum in the warfarin dose being required by the elderly population with concomitant warfarin and amiodarone therapy (200 mg/d).

Conclusions. Elderly patients (age >65 years) are more sensitive to warfarin therapy.

The clinical caveats in the elderly include reduced starting doses, elimination of unnecessary medications and anticipating and monitoring for drug interactions, especially when prescribing warfarin and amiodarone.

SANTRAUKA

Reikšminiai žodžiai: varfarinas, vaistų sąveika, antikoaguliantai, dozės.

Varfarinas yra dažniausiai gydytojų išrašomas geriamasis antikoaguliantas. Dėl esminių pacientų grupių jautrumo skirtumų, vartojant šį preparatą gali pasireikšti skirtingas terapinis rezultatas, yra kraujosruvų pavojus. Dėl šių priežasčių būtinas sisteminis požiūris į kiekvieno paciento, vartojančio antikoaguliantus, stebėseną.

Tyrimo tikslas. Nustatyti ir apibendrinti dažniausiai pasitaikančius galimus varfarino sąveikos su kitais ligoninės kardiologijos skyriuje senyviems pacientams išrašomais vaistais atvejus.

Medžiaga ir metodai. Šiame tyrime dalyvavusių pacientų amžius virš 65 m. Ligoninės kardiologijos skyriuje jie buvo gydomi varfarinu nuo 2008 m. gegužės iki rugsėjo mėn.

Rezultatai. Tyrimo imtis – 100 pacientų (60 vyrų, 40 moterų) atitiko tyrimų kriterijus. Amžiaus vidurkis buvo 69 ± 3 metai. Pacientams buvo skirta varfarino terapija dėl: prieširdžių virpėjimo (n = 43), kitų ritmo sutrikimų (n = 29), kardiomiopatijos (n = 21), vožtuvų protezų (n = 7).

Buvo analizuojami ir kiti paskirti vaistai, kurie galėjo sąveikauti su varfarinu, pavyzdžiui, amiodaronas (25 proc.), statinai (13 proc.), aspirinas (4 proc.), protonų siurblio inhibitoriaus omeprazolis (4 proc.)

Šiame tyrime nustatytas atvirkštinis koreliacinis ryšys tarp pradinės varfarino dozės ir palaikomosios amiodarono dozės (r2 = 0,94, p < 0,005). Apskaičiavus antikoagulianto dozę šiems pacientams, paaiškėjo, kad ji sumažėjo 32 proc. nuo maksimalios varfarino dozės paskirtos vyresnio amžiaus ligoniams, jei kartu su varfarinu vartojamas ir amiodaronas (200 mg/d).

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Išvados. Senyvi pacientai (amžius> 65 metų) yra jautresni varfarinui.
Klinikiniai perspėjimai gydant pagyvenusius žmones: mažesnės pradinės dozės, nebūtinų medikamentų vengimas, vaistų sąveikos stebėsena, ypač tais atvejais, kai skiriant varfariną išrašomas ir amiodaronas

INTRODUCTION

Warfarin is the most widely prescribed oral anticoagulant used to control and prevent thromboembolic disorders. The number of elderly patients who are eligible to receive warfarin is steadily expanding, in part because of the increasing prevalence of atrial fibrillation. Both the risk of stroke in patients with atrial fibrillation and the risk of mortality in patients who experience a stroke increase with age. Warfarin therapy reduces the risk of stroke in patients with atrial fibrillation by 68 %. It is highly effective for the treatment and prevention of venous and arterial thrombosis [1]. Current European Society of Cardiology (ESC) guidelines for the management of atrial fibrillation recommend that anti-thrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thromboembolism. ESC guidelines offer two risk assessment schemes: $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke (doubled) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 – 74, and sex category (female)) [2]. These schemes are based on a point system which can help to make decision whether or not to anticoagulate.

Synthetic coumarin derivate exerts its anticoagulant effect by inhibiting the cyclic interconversion of vitamin K and thereby impeding the production of clotting factors in the liver [3]. The level of anti-coagulation is expressed as the INR which is derived from the ratio between the actual prothrombin time and that of a standardized control serum. Based on achieving a balance between stroke risk with low INRs and an increasing bleeding risk with high INRs, an INR of 2.0 – 3.0 is the likely optimal range for prevention of stroke and systemic embolism as mentioned in Guidelines of European Society of Cardiology and American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition) [2, 4].

Selection of the right warfarin dose at the treatment is not straightforward. Because of substantial inter-patient differences in sensitivity to warfarin, numerous variables (patient`s nutritional status, gender) that can alter the response to therapy with time, and the potential risk for major hemorrhage, a systematic approach to therapeutic drug monitoring must be carried out for every patient who has anticoagulant therapy [5]. These interactions can be divided into pharmacokinetic and pharmacodynamic effects. Pharmacokinetic mechanisms of drug interaction with warfarin are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. Pharmacodynamic mechanisms for interactions with oral anticoagulant are synergism (impaired hemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and an altered physiologic control loop for vitamin K (hereditary resistance to oral anticoagulants). The major mechanisms of warfarin drug interactions are inhibition of metabolism (amiodarone, omeprazole, statinns), affection of bio-availability, protein binding (digoxin, salicylates) [6, 7].

The most serious interactions with warfarin are those that increase the anticoagulant effect and the risk of bleeding [8, 9]. By using the lowest possible required dose of warfarin, the physician can minimize the risk of bleeding while providing the benefits of anticoagulation.

Warfarin combine 3 unfavorable properties which make them prone to potentially life threatening drug - drug interactions: high plasma protein binding, cytochrome P450 dependent metabolism and narrow therapeutic range [3, 10-12]. It is important to pay attention when combinatorial therapy is appropriate.

The aim of the study was to identify most frequent existent possible warfarin interactions in the hospital drug prescribing, analyze the effects of interactions on the warfarin dose for cardiological elderly patients.

METHODS

In this study patients (age >65) with heart rhythm disorders or other indications for warfarin therapy (for example, thromboembolic complications associated with cardiac valve replacement, prophylaxis and/or treatment of cardiac embolism, pulmonary embolism) from cardiological department of the hospital were included at the time from May 2008 to September 2008. In the questionnaire such facts from patients' medical history as gender, age, indication for oral anticoagulant therapy, presence of other medical diagnoses, used drugs, values of International Normalized Ratio (INR) and dates of testing were summarized.

The warfarin dose was adjusted as necessary to maintain a therapeutic INR, which was defined in the majority of patients as an INR of 2 to 3. In a small subset of patients the INR was maintained between the ranges of 2.5 to 3 and 1.5 to 2.5 for valvular replacement and dilated cardiomyopathy indications, respectively.

In statistical analysis comparisons of mean maximum percentage reductions in the warfarin dose observed during therapy of drugs which potentiate the anticoagulant effect of warfarin were performed using the Students' *t* test. The level of statistical significance was defined as a p value < 0.05; data are expressed as mean ± SD.

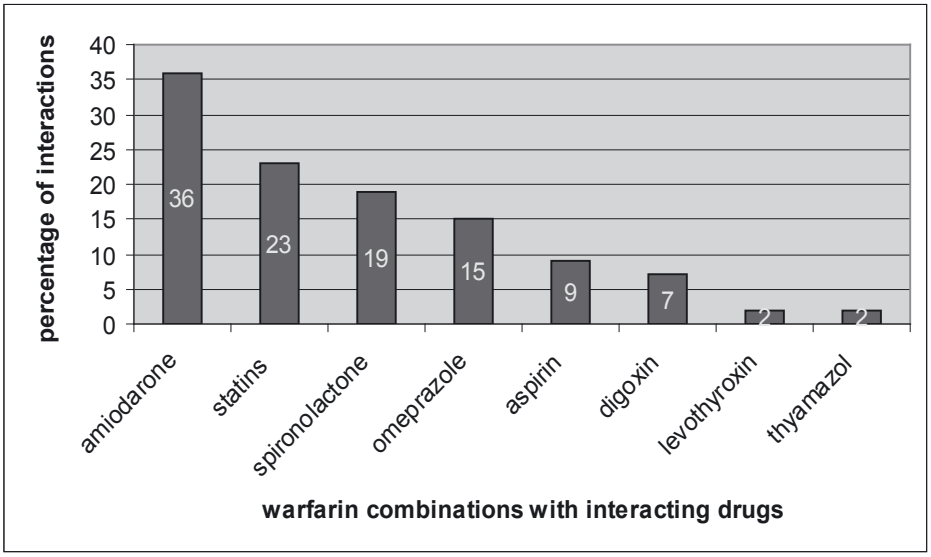

Figure 1. Drug Interactions with Warfarin in the Hospital.

RESULTS

A total of 100 patients (60 male, 40 female) met the study inclusion criteria. The mean age was 69 ± 3 years. Patients received warfarin treatment for the following indications: atrial fibrillation (n = 43), other rhythm disorders (n = 29), cardiomyopathy (n = 21) prosthetic valve (n = 7).

Most frequent other medical diagnosis in study population were chronic heart failure (n = 52), hypertension (n = 32), diabetes [16], renal failure [4].

Concomitant other drugs were analyzed known either to prolong the prothrombin time or INR or to interact with warfarin. There were some frequent combinations of warfarin with other drugs such as amiodarone (25 %), statins (13 %), anti-inflammatory drugs (aspirin (4 %)), proton pump inhibitor (omeprazole (4 %)) (Fig. 1).

Safety of the anti-coagulation in the elderly were maximized through careful monitoring and maintenance of an INR between 2 and 3. Because warfarin dose requirements are known to decrease with age, the mean used dose of warfarin was 6.0 ± 1.2 mg/d ($p < 0.001$). At the same time there were supratherapeutic INR values (> 4.4± 0.4) for many elderly (n = 31).

18 patients of study population with INR values greater the 4.0 had received concomitant amiodarone therapy with maintenance dose 200 mg/d. This interaction has been described in literature. Amiodarone strongly potentiates the anticoagulant effect of warfarin, resulting in prolongation of the INR. In this study we found inverse correlation between starting dose of warfarin and maintenance dose of amiodarone ($r^2 = 0.94$, $p < 0.005$). When we calculated the dose of anticoagulant for these patients, it seemed to be decreased for 32% mean maximum in the warfarin dose being required by the elderly population with concomitant warfarin and amiodarone therapy (200 mg/d).

Patients with statins therapy (n = 23) received atorvastatin (n = 20), rosuvastatin (n = 3). Warfarin – statin combination showed no relevant changes in prothrombin time.

In other cases of potential drug interactions we could not find any statistic significant correlations between the warfarin dose and supratherapeutic INR in our study.

Although a therapeutic INR was maintained throughout the study period, minor bleeding (nose or gum bleeding) occurred in five patients (5 %). No major hemorrhagic episodes were observed in the study population.

Analyzing risk stratification for bleeding in patients with INR values greater then 4.0, association with other clinical diagnosis which is included in bleeding risk score, hypertension (n = 20) and abnormal renal function (n = 2) concomitantly with drugs (amiodarone) could potentiate effect of warfarin needed for regularly following of antithrombotic therapy.

DISCUSSION

The present study demonstrated a clinically significant interaction between amiodarone and warfarin- defined as an INR > 4.4 ± 0.4. Amiodarone is purposed to interact with warfarin by inhibiting CYP and displacing warfarin from protein – binding sites. Because of these properties, amiodarone can increase the INR of patients on stable dosages of warfarin. Also the warfarin – amiodarone interaction is complicated by the prolonged amiodarone loading phase.

For other patients with supratherapeutical INR value we could not find any statistical significant correlations between used combinations of drugs. In this case we must remember about other factors such as genetic, other clinical characteristics which are included in new simple bleeding risk score ((HAS – BLED - hypertension, abnormal renal/ liver function, stroke, bleeding history or predisposition,

labile INR, elderly (>65), drugs/alcohol concomitantly) [2]. One of the study limitation is that we did not analyze other environmental factors which could lead to the INR changes.

Guidelines recommend in elderly patients who are taking medications to increase the sensitivity to warfarin (for example, amiodarone) the using of a starting dose of ≤ 5mg with subsequent dosing based on the INR response (4). In some cases of our study it seems to need reduce warfarin dose to avoid of possible bleeding risk. This fact also require intense monitoring of INR.

In our study statins (atorvastatin, rosuvastatin) did not manifest significant quality to interact with warfarin. In literature we can find information about interaction of more lipophilic statins (fluvastatin, simvastin) with anticoagulant [13, 14]. Atorvastatin and simvastatin appear to differ in their potential to interact with warfarin. Vitamin K antagonist (warfarin) also has minor pharmacokinetic interaction with spironolactone which in our study did not reflect as significant.

CONCLUSIONS

Warfarin dose requirements decrease greatly with age. Lower initiation and maintenance doses should be considered for the elderly (age > 65years).

The clinical caveats in the elderly include elimination of unnecessary medications and anticipating and monitoring for drug interactions, especially when prescribing warfarin and amiodarone.

Especially INR regular monitoring is required during the initiation or discontinuation of the medications.

Clinical pharmacist collaboration with physician is important to:

recognize, analyze and manage potential warfarin – drug interactions during hospitalizations;

prescribe other medications or change doses of warfarin based on changes of INR.

The importance of patient education cannot be overstated. The patient must have an appreciation of the potential for adverse consequences due to other medications or alternative therapies used with warfarin. The clinical pharmacist with other health providers can offer reminders of signs of bleeding, emphasize vigilance in disclosing the usage of nonprescription remedies, promote diligence in medication adherence, and encourage adherence to regular INR monitoring.

Footnotes

Abbreviations: INR = international normalized ratio

There is not any conflict of interest in this study.

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