PERSONALIZĒTA ANTIKOAGULANTU TERAPIJA KARDIOLOĢIJĀ

INDIVIDUALIZED ANTICOAGULATION THERAPY IN CARDIOLOGY

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ABSTRACT

No standard dosage of warfarin will work for all people or even for the same person in all situations. Dosing of this medication must be individualized.

The purpose was to investigate mechanisms of warfarin – drug interactions, identify possible warfarin interactions in the hospital drug prescribing for cardiologic patients.

In this study patients from cardiological department of the hospital were included who received warfarin therapy from May 2008 to September 2008.

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

Concomitant other drugs were analysed known either to prolong the prothrombin time or INR or to interact with warfarin. It is recommended that for patients who received combinations of warfarin with other drugs such as amiodarone (25%), anti-inflamatory drugs (aspirin (4%)), statins (13%), proton pump inhibitor (omeprazole (4%)) the daily warfarin dose is reduced to avoid increased bleeding risk.

CONCLUSIONS

- Risk of warfarin – drug interactions were found for combined use with amiodarone, digoxin, statins, spironolactone, aspirin, omeprazole, thyroid hormones and antithyroid drugs.
- Physician and clinical pharmacist collaboration is important to recognize, analyze and manage potential warfarin – drug interactions during hospitalizations and if necessary prescribe other medications or adjust dose of warfarin.

KEY WORDS: warfarin, drug-drug interactions, anticoagulation, dose.

INTRODUCTION

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 [10]. 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 [6]. 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 who has anticoagulant therapy [1, 2]. Warfarin – drug interactions are often encountered in the care of elderly potentially causing hospital admission and death. 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. Pharmacidynamic 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 most serious interactions with warfarin are those that increase the anticoagulant effect and the risk of bleeding [3, 4]. 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 threating drug - drug intearctions: high plasma protein binding, cytochrome P450 dependent metabolism and narrow therapeutic range [6, 5, 7, 11]. It is important to pay attention when combinative therapy is appropriate.

THE AIM was to investigate mechanisms of warfarin – drug interactions, identify possible warfarin interactions in the hospital drug prescribing, define the effects of interactions on the warfarin maintenance dose for cardiologic elderly patients with an international normalized ratio target between 2.0 and 3.0.

MATERIALS AND METHODS

In this study patients (age >65) from cardiologic department of the hospital were included who received warfarin concomitant with other drugs at the time from May 2008 to September 2008. In the questionnaire such facts from patient`s 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 3.5. and 1.5 to 2.5 for valvular replacement and dilated cardiomyopathy indications, respectively.

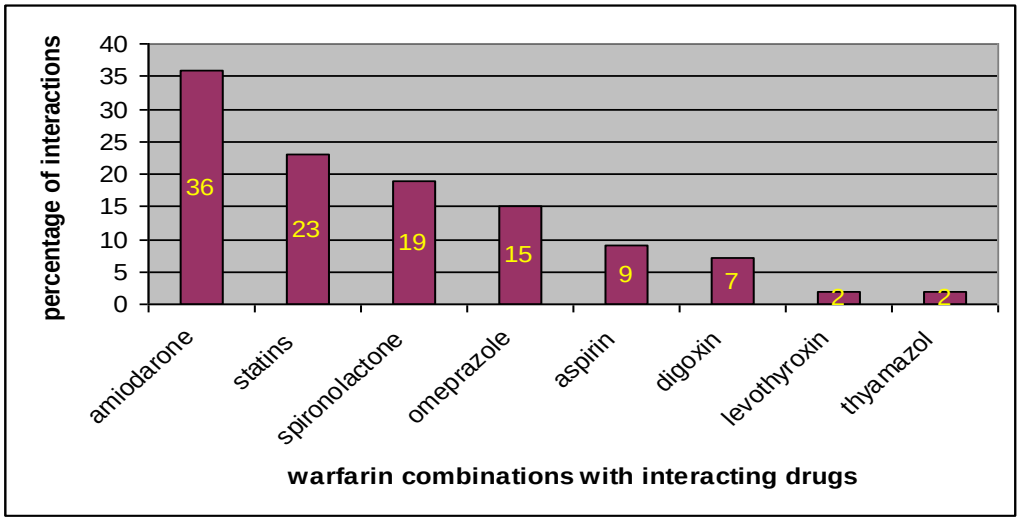
In statistical analysis comparisons of mean maximum percentage reductions in the warfarin dose observed during therapy of drugs which potentiate the anticoagulant effect of warfarin were performed using the Student`s *t* test. The level of statistical significance was defined as a p value <0.05; data are expressed as mean ± SD.

RESULTS

A total of 100 patients (60 male, 40 female) met the study inclusion criteria. The mean age was 71 ± 6 years. Patients received warfarin treatment for the following indications: atrial fibrillation (n=43), tachyarrytmia (n=29), prosthetic valve (n=7), dilated cardiomyopathy (n=21).

Concomitant other drugs were analysed known either to prolong the prothrombin time or INR or to interact with warfarin. It is recommended that for patients who

received combinations of warfarin with other drugs such as amiodarone (25%), anti-inflamatory drugs (aspirin (4%)), statins (13%), proton pump inhibitor (omeprazole (4%)) the daily warfarin dose is reduced to avoid increased bleeding risk (Figure 1). In this study these combinations were found to be associated with a higher prevalence of hemmorrhage compared with warfarin used alone.



1.attēls**. Mijiedarbībā esošo medikamentu raksturojums stacionārā**
Figure 1. **Drug Interactions with Warfarin in the Hospital**

The major mechanisms of warfarin drug interactions are inhibition of metabolism, affection of bioavailability, protein binding (Table 1).

1. tabula/Table 1

Medikamentu mijiedarbības iespējamo mehānismu apkopojums [8, 9]
Mechanism of Selected Warfarin – Drug Interactions [8, 9]

Mechanism of interaction	Examples
Inhibit the metabolism of warfarin	amiodarone (CYP2C9, CYP3A4, CYP1A2) omeprazole (CYP2C19) statins (rosuvastatin, atorvastatin) (CYP2C9)
Displace warfarin from protein – binding sites	digoxin salicylates
Inhibit platelet aggregation	salicylates
Decrease or increase catabolism of vitamin K dependent clotting factors	thyroid hormones and antithyroid drugs
Diminish the ability of warfarin to prevent blood clots because the platelet cells and proteins are more concentrated after removal of sodium and water from the body	spironolactone

Patient`s age, gender, other diseases such as diabetes, hypertension, liver diseases, impairment of coagulation system, history of bleeding, thyroid disorders may effect warfarin sensitivity resulting in increased or decreased warfarin requirements.

Safety of the anticoagulation in the elderly can be 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 starting dose of warfarin 6.0 ± 1.2 mg/d ($p<0.001$) will likely result in supratherapeutic INR values (>3.5) for many elderly (n=31). 27 patients with INR value >3.5 ± 0.2 received concomitant amiodarone maintenance dose 200 mg/d. This interaction has been described in literature. Amiodarone strongly potentiates the anticoagulant effects 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 ($r^2=0.94$, $p<0.005$). With a 32% mean maximum reduction in the warfarin dose being required by the study population at 8 weeks after concomitant warfarin and amiodarone therapy (200mg/d). 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.

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.

On the basis of the available literature all these types of interactions are easily managed by INR monitoring which is required during the initiation or discontinuation of the medications.

DISCUSSION

Many coexisting factors – mechanism of action, pharmacokinetic, pharmacodynamic properties of warfarin, indications, administration, dosage, adverse effects, withdrawal of oral anticoagulant could facilitate prescribing decisions and assist with appropriate monitoring to avoid serious adverse reactions. The mechanism for increased sensitivity to warfarin with aging is not well-understood. Factors such as hypoalbuminemia (leading to reduce volume of distribution), decreased dietary vitamin K intake (resulting in a decreased capacity to synthesize functional clotting factors), reduced absorption of vitamin K, and polypharmacy (producing drug-drug interactions that potentiate warfarin) may lead to increased warfarin sensitivity for an individual patient. The pharmacokinetics of warfarin do not explain the lower dose requirements, because the distribution and elimination half-lives of warfarin change very little with advancing age.

Warfarin-related adverse drug events have significant consequences in the form of bleeding events and associated hospital admissions. The frequency of monitoring and skilful dose adjustment is widely believed to be a significant factor in the success of warfarin therapy.

CONCLUSIONS

1. Coumadin derivates (warfarin) combine 3 unfavourable properties, which make them prone to potentially life threating drug – drug interactions:
   – high plasma protein binding
   – cytochrome P450 dependent metabolism
   – narrow therapeutic range

2. Warfarin plays a significant role in the prevention and treatment of thrombembolic disease among elderly. Elderly patients (age >65 years) are more sensitive to warfarin therapy.
3. Drug interactions and adverse drug reactions increase with increasing numbers of medications prescribed and represent a complex interplay of age, underlying disease, and number and types of medications. 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.
4. Risk of warfarin – drug interactions was found for combined use with amiodarone, digoxin, statins, spironolactone, aspirin, omeprazole, thyroid hormones and antithyroid drugs.
5. Safety of the anticoagulation in the elderly can be maximized through careful monitoring and maintenance of an INR between 2 and 3.
6. 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, amphasize vigilance in disclosing the usage of nonprescription remedies, promote diligence in medication adherence, and encourage adherence to regular INR monitoring.
7. Physician and clinical pharmacist collaboration 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.

FOOTNOTES

Abbreviations: INR = international normalized ratio

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