

A REVIEW ON WARFARIN DRUG INTERACTIONS

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ABSTRACT

Warfarin is an anticoagulant and it may be one of many drugs popularly referred to as a blood thinner, this is a misnomer, since it does not affect the thickness or viscosity of blood. Dosing of warfarin is complicated by the fact that it is known to interact with many commonly used medications and even with chemicals that may be present in certain foods. These interactions may enhance or reduce warfarin anticoagulant effect. In order to optimize the therapeutic effect without risking dangerous side effects such as bleeding, close monitoring of the degree of anticoagulation is required by blood testing like international normalized ratio.

Keywords: Interaction, dose, monitoring.

INTRODUCTION

A drug interaction is defined as the pharmacological or clinical response to the administration or co-exposure of a drug with another substance that modifies the patient's response to the drug (G Kannan et al. 2011).¹ It is reported that 20-30% of all adverse reactions to drugs are caused by interactions between drugs. This incidence increases among the elderly and patients who take two or more medications. The term 'drug interaction' is most often used to describe drug-drug interactions, but there are various substances and/or factors that can alter the pharmacokinetics and/or pharmacodynamics of medications. These include food (Singh BN et al. 2004),² nutritional supplements (Sparreboom A et al. 2004),³ formulation excipients and environmental factors such as cigarette smoking (Ando Y. 2004).⁴ The term drug-drug interactions (DDIs) refer to alteration in the pharmacokinetics or effects of a drug by the presence of another drug (Baxter, 2010).⁵ It can lead to increased toxicity and untoward effects of many drugs e.g., concomitant use of acetaminophen with

isoniazid is associated with higher risk of liver toxicity (Nolan et al. 1994).⁶ Studies have demonstrated that old age, taking increased number of medications, long hospital stay, gender and comorbid conditions are common predictors of DDIs (Doubova et al., 2007; Gagne et al., 2008; Johnell and Klarin, 2007; Juurlink et al., 2003; Katona, 2001; Nobili et al., 2009; Riechelmann et al. 2005).^{7,8,9,10,11,12,13} Interpatient variability is also an important factor that can influence drug interactions. Important variables are gender, age, genetics and/or co-morbid conditions. These can affect patient responses to treatment and the toxicity profile of the agent. Polypharmacy prevails in many chronic diseases (Evans WE, McLeod HL. 2003).¹⁴ Warfarin, a coumarin derivative, produces an anticoagulant effect by interfering with the cyclic interconversion of vitamin K and its 2,3 epoxide (vitamin K epoxide). Vitamin K is a cofactor for the carboxylation of glutamate residues to gamma-carboxyglutamates (Gla) on the N-terminal regions of vitamin K-dependent proteins. These proteins, which include the coagulation factors II, VII, IX, and

X, require γ -carboxylation by vitamin K for biological activity. By inhibiting the vitamin K conversion cycle, warfarin induces hepatic production of partially decarboxylated proteins with reduced coagulant activity. Warfarin also interferes with the carboxylation of Gla-proteins synthesized in bone. Although these effects contribute to fetal bone abnormalities when mothers are treated with warfarin during pregnancy, there is no evidence that warfarin directly affects bone metabolism when administered to children or adults.¹⁵

The warning that there is a potential to enhance the effect of warfarin prolonging the INR with cranberry juice intake is mostly based on faulty reports, many of which are not even case reports but case comments consisting of a few sentences about a possible interaction. On the basis of anecdotal reports, the current study, and other randomized and surrogate trials, there should be no problem with patients taking warfarin drinking average or moderate amounts of cranberry juice. The history of the cranberry juice-warfarin interaction seems to follow a pattern set by other purported interactions with warfarin, including some with antibiotics, in which a temporal relationship appears to exist between the suspected precipitant drug and a change in patient response to warfarin. The cases often lack sufficient detail or include confounders that make it impossible to establish causation. When prospective, controlled studies are done, the interaction is not observed (Zikria J.et.al, 2010).¹⁶

Barbara J. Mason et al conducted a study on A Pharmacokinetic and Pharmacodynamic Drug Interaction Study of Acamprosate and Naltrexone and found that Coadministration of acamprosate with naltrexone significantly increased the rate and extent of absorption of acamprosate, as indicated by an average 33% increase in acamprosate maximum plasma concentration, 33% reduction in time to maximum plasma concentration, and 25% increase in area under the plasma concentration-time curve. Acamprosate did not affect the pharmacokinetic parameters of naltrexone or 6-beta-naltrexol. A complete absence of negative interactions on measures of safety and cognitive function supports the absence of a contraindication to co-administration of acamprosate and naltrexone in clinical practice (Barbara J. Mason.et.al.2002).¹⁷

K U Dinesh et.al carried out a study on Pattern of Potential Drug-Drug Interactions in Diabetic Out-patients. The study found that patients who were taking a higher number of drugs had a greater risk experiencing DDIs. Metformin

and enalapril were the highrisk drugs for DDIs. The hospital Drug Information Center can play an important role in minimizing DDIs in diabetic patients by providing drug-drug interactions (DDI)-related information to prescribers (K U Dinesh et.al.2007).¹⁸

Philip S. Wells.et.al conducted a study on Interactions of Warfarin with Drugs and Food and the study found that many drugs and foods interact with warfarin, including antibiotics, drugs affecting the central nervous system, and cardiac medications. Many of these drug interactions increase warfarin's anticoagulant effect (Philip S. Wells.et.al.1994).¹⁹ Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy was carried out by Gagne JJ, Maio V and Rabinowitz C. Top 3 interactions identified account for 82% of total exposures were Warfarin with NSAIDs, Simvastatin/lovastatin with Amiodarone and Simvastatin/lovastatin with Macrolide antibiotics. The risk of exposure to potentially significant DDIs increased as the number of medications prescribed increased (Gagne JJ, 2008).²⁰

David N. Juurlink.et.al conducted a study on Drug-Drug Interactions Among Elderly Patients Hospitalized for Drug Toxicity. During the 7-year study period, 909 elderly patients receiving glyburide were admitted with a diagnosis of hypoglycemia. In the primary analysis, those patients admitted for hypoglycemia were more than 6 times as likely to have been treated with co-trimoxazole in the previous week (adjusted odds ratio, 6.6; 95% confidence interval, 4.5-9.7). Patients admitted with digoxin toxicity (n = 1051) were about 12 times more likely to have been treated with clarithromycin (adjusted odds ratio, 11.7; 95% confidence interval, 7.5-18.2) in the previous week, and patients treated with ACE inhibitors admitted with a diagnosis of hyperkalemia (n = 523) were about 20 times more likely to have been treated with a potassium-sparing diuretic (adjusted odds ratio, 20.3; 95% confidence interval, 13.4-30.7) in the previous week. No increased risk of drug toxicity was found for drugs with similar indications but no known interactions (amoxicillin, cefuroxime, and indapamide, respectively). Many hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions. Many of these interactions could have been avoided (David N. Juurlink.et.al.2003).²¹

Nobili A.et.al carried out a study to estimate the prevalence of potentially severe drug-drug interactions (DDIs) and their relationship with age, sex and number of prescribed drugs. The

study identified the prevalence of potentially severe DDIs was 16%, and rose with increasing patient's age and number of drugs prescribed. At multivariate analysis, the adjusted odds ratios rose from 1.07 (95% CI 1.03-1.11) in patients aged 70-74 to 1.52 (95% CI 1.46-1.60) in those aged 85 or older. Elderly taking more than five drugs on a chronic basis had a statistically significant higher risk of severe DDIs than those receiving less than 3 or 3-5 such drugs. As physicians still have some difficulty in managing this problem, it is essential to highlight for them, which factors raise the risk of DDIs (Nobili A.et.al. 2009).¹²

Chunliu Zhan et al. carried out Retrospective assess the prevalence and correlates of potentially harmful drug-drug combinations and drug-disease combinations prescribed for elderly patients at outpatient settings. The results shows that 0.74% (95% confidence interval (CI)=0.65–0.83) of visits with two or more prescriptions had at least one inappropriate drug-drug combination, and 2.58% (95% CI=2.44–2.72) of visits with at least one prescription had one or more inappropriate drug-disease combinations. Of visits with a prescription of warfarin, 6.60% (95% CI=5.46–7.74) were prescribed a drug with potentially harmful interaction. Of patients with benign prostatic hypertrophy, 4.06% (95% CI=3.06–5.06) had at least one of six drugs that should be avoided. The number of drugs prescribed is most predictive of inappropriate drug-drug and drug-disease combinations (Chunliu Zhan et al.2005).²²G Kannan.et.al conducted a study on drug-drug interactions in cancer patients of a south Indian tertiary care teaching hospital. The results shows, out of 75 patients (32 males and 43 females; median age 56 years, age range 23-74) were enrolled in the study and their prescriptions were screened. 213 interactions were identified of which, 21 were major, 121 were moderate and 71 were minor. There were 13 (6.1%) clinically significant interactions between anticancer drugs and 14 (6.5%) drug-drug interactions between anticancer drugs and other drugs prescribed for co-morbidities. There was a positive correlation between number of drugs prescribed and drug interactions (P=0.011; OR 0.903). Though there was not any life threatening interactions, the potential interactions were brought to the oncologist purview for ensuring patients safety and to avoid undesirable effects (G Kannan.et.al.2011).¹

Svetlana V Doubova.et.al. were conducted a study on Potential drug-drug and drug-disease interactions in prescriptions for ambulatory

patients over 50 years of age in family medicine clinics in Mexico City. The study found that the average number of prescribed drugs was 5.9 ± 2.5 . About 80.0% of patients had prescriptions implying one or more potential drug-drug interactions and 3.8% of patients were prescribed drug combinations with interactions that should be avoided. Also, 64.0% of patients had prescriptions implying one or more potential drug disease interactions. The factors significantly associated with having one or more potential interactions included: taking 5 or more medicines (adjusted Odds Ratio (OR): 4.34, 95%CI: 2.76–6.83), patient age 60 years or older (adjusted OR: 1.66, 95% CI: 1.01–2.74) and suffering from cardiovascular diseases (adjusted OR: 7.26, 95% CI: 4.61–11.44).The high frequency of prescription of drugs with potential drug interactions showed in this study suggests that it is common practice in primary care level. To lower the frequency of potential interactions it could be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events (Svetlana V Doubova.et.al.2007).²⁴

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