SHORT INVITED LECTURES
KRATKA VABLJENA PREDAVANJA

DRUG INTERACTIONS WITH CARBAMAZEPINE: A CASE STUDY OF INFLUENCE ON ANTICOAGULATION TREATMENT WITH WARFARIN

INTERAKCIJE ZDRAVIL S KARBAMAZEPINOM: PRIMER RAZISKAVE VPLIVA NA ANTIKOAGULACIJSKO ZDRAVLJENJE Z VARFARINOM

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Abstract

Background — *Drug interactions are an important segment of drug related problems. Therefore their evaluation should be an integral component of patient management, especially in elderly patients who often receive multiple medications. In this manuscript drug interactions with emphasis on their relevance and mechanism are reviewed. Additionally, as an example a detailed analysis of induction of warfarin metabolism during co-treatment with carbamazepine is presented.*

Patients and methods — *We searched MEDLINE and tertiary sources. 188 patients on warfarin therapy in the maintenance phase were retrospectively analysed to study the interaction of carbamazepine with warfarin. Blood plasma concentrations of warfarin enantiomers and their metabolites were measured by high performance liquid chromatography.*

Results — *In patients co-treated with carbamazepine daily warfarin dose necessary to maintain INR in the range between 2.0 in 3.0 was significantly higher (9.00 versus 4.07 mg/day). Despite the difference in daily dose requirement plasma concentrations of warfarin enantiomers were similar, due to the enhanced metabolism of predominantly R-warfarin by cytochrome P450 (CYP) 3A4. Consequently, the concentration of 10-hydroxywarfarin, which is formed by CYP3A4 was 9-times higher.*

Conclusions — *With this study relevance and mechanism of carbamazepine interaction with warfarin was assessed. The study confirmed that the need for warfarin dosage adjustment during initiation and discontinuation of carbamazepine treatment is caused by induction of warfarin metabolism, predominantly by CYP3A4.*

Key words — *drug interactions; drug related problems; warfarin; carbamazepine; metabolism; induction*

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Izvleček

Izhodišča *Interakcije med zdravili predstavljajo pomemben del težav povezanih z zdravili. Njihovo prepoznavanje mora zato biti sestavni del obravnave bolnikov, zlasti starostnikov, ki običajno jemljejo več zdravil sočasno. V prispevku je podan pregled interakcij med zdravili s stališča njihovega kliničnega pomena in mehanizma. Podrobneje je predstavljena indukcija presnove varfarina pri sočasnem zdravljenju s karbamazepinom.*

Bolniki in metode *Literaturne podatke smo zajemali iz zbirke MEDLINE in terciarnih virov. V retrospektivno raziskavo interakcije med karbamazepinom in varfarinom smo vključili 188 bolnikov v vzdrževalni fazi zdravljenja z varfarinom. Bolnikom smo s tekočinsko kromatografijo visoke ločljivosti v krvni plazmi določili koncentracijo obeh enantiomer varfarina in njunih presnovkov.*

Rezultati *Pri vključenih bolnikih, ki so bili sočasno zdravljeni s karbamazepinom, smo ugotovili, da so dnevni odmerki varfarina potrebni za vzdrževanje INR v intervalu med 2,0 in 3,0 značilno večji (9,00 proti 4,07 mg/dan), kljub temu pa so plazemske koncentracije obeh enantiomer varfarina podobne. Vzrok za to je pospešena presnova zlasti R-varfarina preko citokroma P450 (CYP) 3A4. Posledično je bila 9-krat povišana tudi koncentracija 10-hidroksivarfarina, ki nastaja s CYP3A4.*

Zaključki *Z našo raziskavo smo opredelili pomen in mehanizem interakcije med karbamazepinom in varfarinom. Potrdili smo, da je vzrok za potrebo po povečanju odmerka varfarina pri uvedbi zdravljenja s karbamazepinom in zmanjšanja pri njegovi odtegnitvi indukcija presnove predvsem s CYP3A4.*

Ključne besede *interakcije med zdravili; težave povezane z zdravili; varfarin; karbamazepin; metabolizem; indukcija*

Introduction

Drug interactions have been studied, interpreted and managed ever since medicines have been concomitantly administered to patients and literature reports have been documented as far back as Index Medicus was catalogued.[1] Currently, thousands of drug interactions are studied each year, contributing to an enormous knowledge base describing simple and complex alterations that occur when drugs are used in combinations.

A drug interaction is defined as clinical response to the drug caused by concomitant drug treatment, dietary factors or social habits such as tobacco or alcohol, different from that anticipated from the known effects of the two agents given alone.[2] This difference is caused either by an alteration in drug pharmacokinetics and/or drug pharmacodynamics. Although drug interactions may also benefit the patient as in concomitant use of ampicillin and probenecid, which has been used for years to achieve high antibiotic concentrations, the term generally has a negative connotation.[3] Nowadays drug interactions are generally recognised as an important subset of adverse drug events and have been emphasized by the media, policy makers and healthcare providers.[4]

Assessment of drug interactions should be an integral component of patient management, especially in elderly patients who receive multiple medications for various diseases. A significant prevalence of drug interactions was found among hospitalised elderly patients.[5, 6] Drug interactions were found to affect more than 20 % of these patients and further, 2 % of the prescriptions were found potentially hazardous, of which more than a half were deemed avoidable.[5] Additionally, patients who receive their care from more than one physician and their medications from more than one pharmacy are also more prone to drug interactions.[7]

The undesirable effect of a drug interaction may arise from a lack of understanding of, or a failure to recall the mode of action and the pharmacokinetics of each drug. Many of undesirable drug interactions are therefore potentially avoidable.

Several checks during the medication process can be used to prevent drug interactions. Of these the most systematically applied is at the pharmacy level.[8] Pharmacies nearly always use computer systems for maintaining records and relaying claims for reimbursement to health insurance providers. This system is also used for screening the prescribed medications for potential drug interactions and other problems and alerts the pharmacist to them.

The possibilities for interactions among drugs are almost limitless. Yet few of these interactions are of a type or of a sufficient magnitude to be clinically important. Many drug interactions do not affect either the unbound drug concentration or the therapeutic activity of the drugs involved. Furthermore, changes in many affected processes are to minor to be of concern.[3] A drug interaction is likely to be detected only when the interacting drug is initiated or withdrawn,

as given the usual variability of responses to drugs it is unlikely that a drug interaction would be detected in a patient stabilised on drug causing the interaction. Although drug dosing regimen would be different in this patient than would be in the absence of the interfering drug, the resulting regimen may still be within the normal range. In this case, the interaction can be detected only if the interacting drug is withdrawn from patient stabilised on drug combination, or if interfering drug is administered to the patient stabilised on monotherapy with the original drug.

Classifications of drug interactions

Drug interactions can be classified based on their severity and on the probability that the interaction exists.[7] Severity is usually classified as minor, moderate, or severe. Drug interactions classified as minor usually have limited clinical consequences and require no change in therapy. Paracetamol, for example may reduce the effect of furosemide, however, it is unlikely to cause any clinical effects or warrant a change in dose.[9] A moderate drug interaction would be the increased incidence of hepatitis with combined therapy with rifampicin and isoniazid. Although the increased incidence of toxicity with this combination is clearly known, it is still used with frequent monitoring of liver enzymes. A severe drug interaction would involve potentially serious toxicity and requires a change in drug, dose or dosing schedule. An example is oversedation observed with midazolam when combined with ketoconazole.[10] Severe drug interactions require discontinuation of one of the co-administered drugs.

In the drug development phase, European Medicines Agency (EMEA) differentiates between detectable and clinically relevant drug interactions, where drug interaction is defined as clinically relevant, when the efficacy and/or toxicity is changed to such an extent that a dosage adjustment or other medical intervention may be required, when the interacting drugs are used as therapeutically recommended.[2]

The likelihood that an interaction is caused by a drug is usually classified as established, probable, suspected, possible, or unlikely. This is determined by documentation of similar interactions in published clinical, pre-clinical and in vitro studies and case reports.

Mechanisms of drug interactions

Although the above classification of drug interactions is clinically useful, it does not define the mechanism of the interaction. Drug interactions can be classified mechanistically on the basis of whether pharmacokinetics or pharmacodynamics is altered. Distinction between the two is made by relating response to the unbound plasma concentration of the pharmacologically active drug moiety. A change in the unbound concentration–time curve implies a pharmacokinetic drug interaction, which can arise either at drug absorption, distribution, metabolism, or elimination through a physical interaction, such as competition for metabolic enzymes, or through altered physiology, such as altered blood flow at drug absorption site. The result is a change in one or more of pharmacokinetic parameters, drug absorption rate constant, bioavailability, distribution volume and clearance.

A number of mechanisms can affect drug absorption including a change in gastric pH, chelation, ion exchange, change in gastric motility, alteration in intestinal flora, modulation of transport proteins or inhibition of intestinal enzymes. Certain drugs, such as ketoconazole, require acidic pH for optimal dissolution and subsequent absorption in the small intestine. Co-administration with proton pump inhibitors, H_2 receptor antagonists, and antacids, which raise gastric pH, markedly reduces the absorption and plasma concentration of this antifungal drug.[11] Combination of ketoconazole with ranitidine led to a reduction in the area under the plasma concentration versus time curve (AUC) by over 50 % which can result in therapeutic failure.[11] Chelation is the irreversible binding of drugs in gastrointestinal tract. Tetracyclines have long been reported to bind with antacids, leading to inactivation. Quinolone antibiotics also chelate with di- and tri-valent cations such as the aluminium and magnesium in antacids, calcium in dairy products, and ferrous sulphate in iron replacement agents.[3] Although these interactions are clinically relevant, they can be avoided by administering the antibiotic two hours before the antacid and no change in dose is necessary. A large number of drugs have been reported to interact with the anionic exchange resins such as cholestyramine.[3] These exchange resins form insoluble complexes with warfarin, digoxin, beta-blockers, nonsteroidal anti-inflammatory drugs, and other, thereby decreasing their absorption and leading to lower plasma concentrations.

The extent to which displacement of drug from plasma protein binding sites result in clinically significant drug interactions has been largely overstated.[12] Based on theoretic arguments using a systematic approach of drug exposure and equilibration time concepts[12] very few drugs interactions have been identified based on this mechanism, and many that have been previously thought to be protein binding interactions have been identified as being metabolically based.

Most drugs undergo biotransformations via Phase I and/or Phase II metabolic reactions. Many Phase I reactions, such as dealkylation, deamination and hydroxylation involve the cytochrome P450 (CYP) monooxygenases. Research on CYP isoenzymes has grown exponentially in the past decade. Advances in the application of scientific methods to identify the amino acid sequences of specific CYP isoenzymes has promoted the research in drug metabolism as well as the identification of specific genetic polymorphisms for these isoenzymes. Additionally, the ability to fully characterize the CYP metabolism of drugs, largely through *in vitro* methods using drug probes and cDNA expressed isoenzymes in human liver microsomes, has brought further understanding to the mechanisms of metabolic drug interactions.[7]

Phase II conjugation reactions, such as glucuronidation and sulphation, involve the microsomal uridine

diphosphate (UDP) glucuronosyltransferases and the cytosolic sulphotransferases, respectively. Although drug interactions involving Phase II enzymes can occur, much less research has been carried out in this area.

Fourteen families of CYP enzymes common to all mammals have been identified.[13] However, only three of these families (CYP1, CYP2 and CYP3) are thought to be important in metabolism of drugs. Isoenzymes within these families that have been identified as important in drug metabolism include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Of these isoenzymes CYP3A4 is the most abundant, constituting 25 % of total hepatic CYP.[14] This isoenzyme is responsible for the metabolism of a large group of structurally diverse drugs. This broad substrate specificity coupled with its expression in intestinal wall, may be responsible for metabolism of the majority of xenobiotics.

Table 1 lists drugs as substrates, inhibitors and inducers of various isoenzymes.[15] Although it can be used as a basic guide to predict drug interactions involving CYP isoenzymes, many variables are not included that would assist the interpretation of clinical significance of these interactions. A drug, which is a substrate for a particular isoenzyme may be considered as an inhibitor of that isoenzyme. However, the converse is not necessarily true. Quinidine, for example, is the most potent inhibitor of CYP2D6, but is metabolised by CYP3A4.

CYP inhibition can be characterised as reversible or irreversible. Drug interactions most commonly involve reversible inhibition and enzyme function is generally regained after one half-life of inhibiting drug, after its discontinuation. Reversible inhibition can be further differentiated to competitive, noncompetitive and uncompetitive mechanism. Competitive inhibition is the most common type, which occurs when the inhibitor prevents substrate binding by binding to active site of free enzyme. Time course of inhibition follows the half-life of inhibiting drug. However, the onset of drug interaction depends on half-life of drug which is being inhibited and can be as long as 5 half-lives away from the moment when the inhibiting drug reaches its steady state (Figure 1).

Although CYP inhibition leads to increased drug concentrations, the following questions need to be considered to assess clinical relevance of interaction[7]: (i) What is the therapeutic index and toxic potential of the drug?; (ii) Which other metabolic pathways are

Table 1. *Selected CYP substrates, inhibitors and inducers. Adapted from[15].*

Razpr. 1. *Izbrani substrati, inhibitorji in induktorji CYP. Prirejeno po[15].*

Substrates				
1A2	**2C19**	**2C9**	**2D6**	**3A4,5,7**
clozapine imipramine naproxen theophylline	**PPIs**: omeprazole lansoprazole pantoprazole rabeprazole **AEDs**: diazepam phenytoin phenobarbitone amitriptyline clomipramine cyclophosphamide progesterone	**NSAIDs**: diclofenac ibuprofen piroxicam **Angiotensin II Blockers**: irbesartan losartan fluvastatin glipizide naproxen phenytoin sulfamethoxazole tamoxifen tolbutamide torsemide warfarin	**Beta Blockers**: S-metoprolol propafenone timolol **Antidepressants**: amitriptyline clomipramine desipramine imipramine celecoxib **Antipsychotics**: haloperidol risperidone thioridazine codeine dextromethorphan duloxetine ondansetron tamoxifen tramadol venlafaxine	**Macrolide antibiotics**: clarithromycin, erythromycin **Anti-arrhythmics**: quinidine **Benzodiazepines**: alprazolam, diazepam, midazolam, triazolam **Immune Modulators**: cyclosporine, tacrolimus paroxetine **HIV Protease Inhibitors**: indinavir, ritonavir, saquinavir **Antihistamines**: astemizole, chlorpheniramine **Calcium Channel Blockers**: amlodipine, diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, verapamil **HMG CoA Reductase Inhibitors**: atorvastatin, cerivastatin, lovastatin, simvastatin aripiprazole, buspirone, cisapride, haloperidol, imatinib, methadone, pimozide, quinine, sildenafil, tamoxifen, trazodone, vincristine
Inhibitors				
1A2	**2C19**	**2C9**	**2D6**	**3A4,5,7**
cimetidine fluoroquinolones fluvoxamine ticlopidine	fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole ticlopidine	amiodarone fluconazole isoniazid	amiodarone chlorpheniramine cimetidine clomipramine fluoxetine haloperidol methadone paroxetine quinidine ritonavir	**HIV Protease Inhibitors**: Indinavir, nelfinavir, ritonavir amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, mibefradil, nefazodone, troleandomycin verapamil
Inducers				
1A2	**2C19**	**2C9**	**2D6**	**3A4,5,7**
tobacco		rifampin secobarbital		carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, troglitazone

AED – antiepileptic drug, NSAID – non steroidal antiinflamatory drug, PPI – proton pump inhibitor

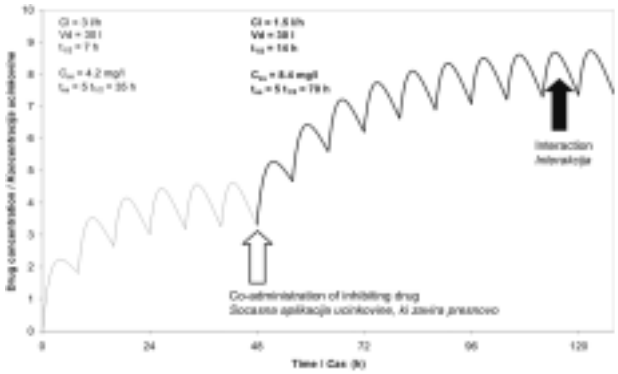

Figure 1. *Onset of drug-drug interaction following co-administration of drug inhibiting drug metabolism at time 48 hours. Due to reversible inhibition of drug metabolism, clearance (Cl) is decreased by 50 % resulting in new steady-state with doubled average drug concentrations (C_{ss}). If distribution volume (Vd) remains unchanged, the new half-life ($t_{1/2}$) is also doubled. As it takes 5 half-lives before the drug reaches its new steady-state, the onset of drug interaction can be far away in time from the moment of inhibiting drug administration (almost 3 days in this case).*

Sl. 1. *Pojav interakcije med zdraviloma po aplikaciji zdravilne učinkovine, ki zavira presnovo, ob času 48 ur. Zaradi reverzibilne inhibicije presnove se očistek (Cl) zmanjša za 50 %, kar vodi do novega stacionarnega stanja z dvakrat večjimi koncentracijami (C_{ss}). Če ostane volumen porazdelitve nespremenjen, se dvakrat podaljša tudi biološka razpolovna doba ($t_{1/2}$) učinkovine. Ker je za vzpostavitev novega stacionarnega stanja potrebnih 5 bioloških razpolovnih dob, je pojav interakcije lahko močno zamaknjen glede na čas, ko odmerimo zdravilo (v tem primeru skoraj 3 dni).*

involved in the drug metabolism?; (iii) Are metabolites pharmacologically active?; (iv) What is the consequence of metabolic inhibition of the metabolites?; (v) Are multiple CYP isoenzymes inhibited?; (vi) Is the patient a poor metaboliser of an isoenzyme for which the inhibitor is specific?; (vii) Do otherwise pharmacologically inert metabolites of the inhibitor inhibit CYP isoenzymes?; and finally (viii) Is the inhibition potentially harmful or helpful?

The direct cause of induction of drug metabolism is increased DNA transcription and synthesis of CYP enzymes. With the exception of CYP2D6, all CYP enzymes are inducible. As with CYP inhibition, there are many clinical consequences possible. Addition of an inducer will decrease drug concentration and therapeutic failure may result. On the other hand, discontinuation of inducer will increase drug concentration in a time-dependant manner and toxicity may result. CYP induction may also accelerate formation of reactive metabolites which may be harmful. There are many mechanisms of enzyme induction identified: induction by the aryl hydrocarbon receptor, ethanol, peroxisome proliferators, the constitutive androstane receptor (CAR) and the pregnane X receptor (PXR).[16]

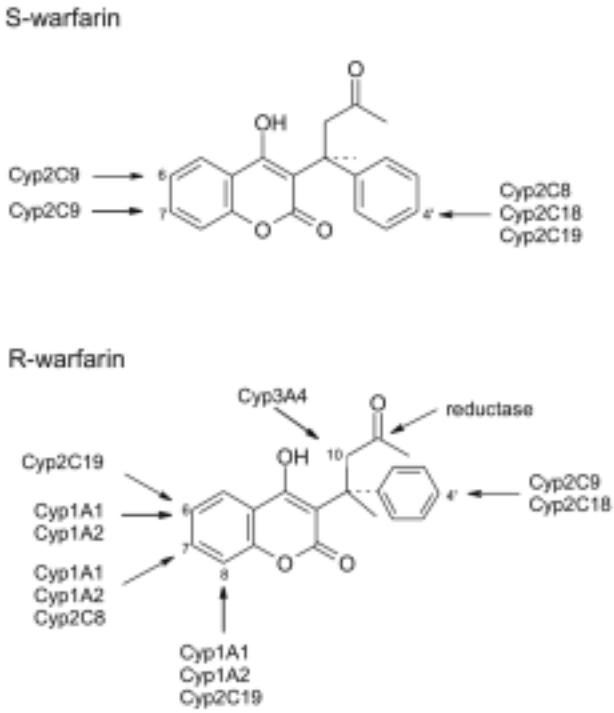

Figure 2. *Main metabolic pathways of warfarin. Arrows mark monohydroxylation at positions 4', 6, 7, 8 and 10 by CYP isoenzymes and reduction of the side chain keto group.*

Sl. 2. *Glavne poti presnove varfarina. S puščicami so označena mesta monohidroksilacije 4', 6, 7, 8 in 10 s CYP izoencimi in redukcija stranske keto skupine.*

Influence of carbamazepine on anticoagulation treatment with warfarin

Warfarin is a coumarin derivative used as an oral anticoagulant drug in the treatment and prevention of thromboembolism. In addition to narrow therapeutic interval and significant interindividual variability in daily dose requirement, numerous drug-drug interactions often complicate treatment and over- or under- anticoagulation frequently occur.[17, 18] Careful monitoring of coagulation by measuring international normalized ratio of prothrombin time (INR) is necessary to tailor the treatment to individual patient, mainly due to complex pharmacokinetics. The asymmetric carbon at position 9 of warfarin gives rise to two enantiomers, R- and S-warfarin, with distinct pharmacological properties (Figure 2).

Following oral administration of a warfarin racemic mixture concentrations of enantiomers in blood plasma differ because of stereoselective metabolism. The plasma clearance of two to five times more potent S-warfarin is approximately twice that of R-warfarin.[19-21] The predominant metabolic reaction is hydroxylation at position 6, 7, 8, 10 and 4' by cytochromes P450 (CYP) leading to a series of inactive monohydroxylated metabolites. Another important route of warfarin metabolic deactivation is reduction of the side chain keto group by carbonyl reductases.[22] Warfarin

metabolism is further characterized by a process termed regioselective metabolism and enantiomers considerably differ in sites of hydroxylation and CYP enzymes involved. The more potent S-warfarin undergoes substantial 7-hydroxylation although 6S- and 4'S-hydroxywarfarin are also formed. On the other hand R-warfarin is metabolized to all five hydroxywarfarin metabolites, of which 6R- and 10R-hydroxywarfarin are the most abundant.[22] The reduction of side chain keto group is prevalent in R-warfarin. It leads to generation of two inactive diastereomeric alcohols; major R,S(+)alcohol and minor R,R(+)alcohol.[22] Moreover, warfarin treatment depends on presence of specific polymorphisms in the *CYP2C9,* vitamin K 2, 3 epoxide reductase system (*VKORC1),* γ-glutamyl carboxylase (*GGCX)* and apolipoprotein E *(ApoE)* genes.[23]

Carbamazepine is due to relatively low behavioural and psychological toxicity and infrequent serious adverse effects still the first line antiepileptic drug for simple or complex partial and generalized tonic-clonic seizures. Additionally, it is commonly used for pain relief in trigeminal and glossopharyngeal neuralgia.[24, 25]

Owing to the poor solubility in water, absorption of carbamazepine following peroral administration is slow and highly variable. Carbamazepine undergoes extensive metabolism and presently 33 different metabolites were identified, but the predominant pathway is formation of equipotent CBZ-10,11-epoxide by CYP3A4. Minor pathways of carbamazepine metabolism include oxidation by CYP1A2 and CYP2C8 isoenzymes.[26] Carbamazepine induces many enzyme systems including CYP1A2, 2C and 3A and glucuronosyltransferase. Consequently, it increases metabolism of many drugs, including its own. With multiple dosing its clearance increases due to autoinduction, which usually begins 3 to 5 days following initiation of treatment and completes in 20 to 35 days.[26] Carbamazepine pharmacokinetics in this period is therefore time-dependent, with a half-life changing from 25 - 65 h after a single dose, to 12 - 17 h during steady-state in the post-induction phase[24, 25, 27] leading to a progressive decrease in carbamazepine plasma levels.

In our previous studies we systematically investigated the influence of CYP2C9 genotype, age, body weight and co-treatment with drugs that interfere with warfarin metabolism on warfarin clearance and daily dose required to keep the international normalised ratio of protrombin time (INR) between 2 and 3 in a large homogenous group of patients (n = 188) in the stable maintenance phase of warfarin therapy.[28] Our results were in agreement with the findings that *CYP2C9*2* and *CYP2C9*3* alleles were associated with a reduction in S-warfarin clearance. Additionally, co-treatment with inducers (primidone, carbamazepine) and potent inhibitors (fluvastatin, amiodarone, gemfibrozil, fenofibrate, losartan) of warfarin metabolism and patient body weight were found to have significant influence on S-warfarin clearance. The two most influential factors for R-warfarin clearance were co-treatment with warfarin metabolism inducers and age. Concomitant treatment with potent inhibitors, lean body weight and plasma albumin concentration were also found to affect R-warfarin clearance. A correlation analysis revealed that 38 % of the interindividual variability of warfarin maintenance dose resulted from differences in S-warfarin clearance, while the rest could be attributed to interindividual variability in the pharmacodynamic phase[28], where polymorphisms in genes involved in blood coagulation have an important role.[29] In the subsequent study, warfarin pharmacokinetics and its influence on dose requirement in patients that were co-treated with carbamazepine (n = 5) were investigated.[30] Only patients with *CYP2C9*1/*1* genotype on stable maintenance warfarin therapy were selected for the analysis to eliminate the influence of *CYP2C9* polymorphisms on warfarin pharmacokinetics and to obtain more homogenous study group. Pharmacokinetic analysis was performed on the basis of measured plasma levels of warfarin enantiomers and hydroxylated metabolites.[31] Interaction consequences were provided for two metabolic pathways, a CYP2C9 selective formation of 7-hydroxywarfarin from S-warfarin and a CYP3A4 selective metabolism of R-warfarin to 10-hydroxywarfarin. Patients co-treated with carbamazepine required significantly higher warfarin dose (median: 9.00 mg/day) than patients treated with warfarin alone (median: 4.07 mg/day). Although groups of patients differed regarding warfarin dose, plasma S- and R-warfarin concentrations were not significantly different, since both S- and R-warfarin clearances were significantly higher. Additionally, patients co-treated with carbamazepine had significantly higher plasma 10-hydroxywarfarin concentrations (median: 0.327 μg/ml) as compared to those treated with warfarin alone (median: 0.036 μg/ml), indicating that carbamazepine influences warfarin metabolism predominantly through the induction of CYP3A4 enzyme. This finding is in agreement with the observed higher clearance of R-warfarin. On the other hand, concentrations of 7-hydroxywarfarin, which is the major metabolite of S-warfarin and is formed almost exclusively by CYP2C9[22], were not significantly different between the two groups of patients. However, higher clearance of S-warfarin in carbamazepine co-treated group was observed. This may be due to only moderate influence of carbamazepine on CYP2C9 activity, which due to limitations of the assay prevented the observation of the expected rise in 7-hydroxywarfarin.[30]

Despite the fact that warfarin and carbamazepine are used for more than 50 years the literature documenting warfarin-carbamazepine interaction is scarce. To our knowledge this is the only study in which its mechanism was evaluated by measuring plasma concentrations of warfarin enantiomers and their metabolites. The results obtained provide further insight into recent case report[32] of patient with paroxysmal atrial fibrillation taking warfarin for stroke prevention. For 5 years her INR was within therapeutic range with a dose of warfarin 30 mg/week. At a visit to her dentist, the patient was prescribed carbamazepine 200 mg/day for control of facial nerve pain. Approximately 2 weeks later her INR declined from 3.3 to 1.3. This change required an 80 % increase in warfarin dose to

maintain INR within 2.0 to 3.0. When adequate warfarin dose was reached carbamazepine was discontinued and resulted in 95 % increase in INR. Consequently resumption to her previous warfarin dosing was needed. This case report demonstrates the impact of both starting and discontinuation of carbamazepine therapy in patient with warfarin therapy.

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