Observational Study of the Inter-Individual Variability of the Plasma Concentrations of Direct Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) and the Effect of rs4148738 Polymorphism of ABCB1

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Abstract: *Background and Aim*: Direct oral anticoagulants (DOACs, i.e dabigatran, rivaroxaban, apixaban) can be administered in fixed doses without laboratory monitoring, however pharmacokinetic and pharmacodynamic characteristics indicate that clinical, demographic and pharmacogenetic factors can influence DOAC antithrombotic efficacy. The aim of this study was to establish the inter-individual variability of DOAC plasma concentrations and influence of ABCB1 rs4148738 polymorphism on DOAC plasma levels.

Materials and Methods: Patients (n=291) taking DOACs for either venous thromboembolism (VTE) or atrial fibrillation (AF) since at least 7 days were enrolled. Demographic and clinical characteristics were collected at enrollment on a standardized form. Diluted thrombin time was measured for dabigatran and anti-Xa activity for apixaban and rivaroxaban on plasmas obtained from blood samples collected in sodium citrate after one month at trough and at peak, e.g. at 2 hours after the morning dose. DNA was extracted from peripheral leukocytes for detection of rs4148738 ABCB1 – P-glycoprotein (P-gp) (intronic region G>A) polymorphism.

Results: All DOACs showed a high inter-individual variability for both peak and trough concentrations in the 291 enrolled patients. Dabigatran peak and trough levels were correlated with creatinine clearance. The ABCB1 gene rs4148738 polymorphism was determined in 142 patients and it influenced peak levels of rivaroxaban 20 mg with lower levels in homozygotes for the minor A allele but not those of apixaban. A non significant effect was observed on dabigatran 150 mg bid peak and trough levels of.

Conclusions: The rs4148738 polymorphism of ABCB1 gene of P-gp can influence rivaroxaban peak and trough levels.

Keywords: Direct oral anticoagulants, single nucleotide polymorphism, pharmacogenetics, P-glycoprotein, atrial fibrillation, venous thromboembolism.

INTRODUCTION

Oral anticoagulant agents, such as vitamin K antagonists (VKA e.g. warfarin), have been the mainstay of prophylaxis and treatment of thromboembolic diseases for several decades [1,2]. Direct oral anticoagulants (DOACs) are direct selective inhibitors of a single coagulation factor either Factor IIa (FIIa) for dabigatran or Factor Xa (FXa) for rivaroxaban, apixaban and edoxaban. DOACs are now available for the prevention of cardioembolism in non valvular atrial fibrillation (AF) and for venous thromboembolism (VTE) prevention and treatment [3]. Clinical trials have shown that DOACs can be administered in fixed doses, without the strict laboratory monitoring required for VKA, thus simplifying oral anticoagulation management. However, DOAC pharmacokinetic and pharmacodynamic characteristics indicate that clinical, demographic and pharmacogenetic factors can influence their anticoagulant effect [4,5]. In all clinical trials comparing DOACs with warfarin for AF or VTE, dose reduction in case of advanced age, lower weight and reduced renal function has been adopted [6-15]. Even in young healthy volunteers, DOACs such as dabigatran have shown a varying degree of inter-individual variability of both pharmacokinetics (coefficient of variation -CV:≈ 30%) and pharmacodynamics (CV ≈ 10%) [16]. The inter-individual differences observed in drug responses could be partially explained by heritable variations in the genes coding for components of the drug use cycle, transporters, receptors and metabolizing enzymes [17]. In particular all DOACs are substrates for the cellular transmembrane transporter P-glycoprotein (Permeability glycoprotein, abbreviated as P-gp), that transports chemicals out of cells and/or are metabolized by cytochrome P450 (CYP450) enzymes. P-gp, also known as multi drug-resistance protein 1 (MDR1) ATP-binding cassette sub-family B member 1 (ABCB1) is a glycoprotein encoded in humans by the

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ABCB1 gene [5]. It is a 160-kDa ATP dependent drug efflux pump for xenobiotic compounds which transports a wide variety of substrates across extra- and intracellular membranes. It is responsible for decreased drug accumulation in multi drug-resistant cells and it is expressed in the intestinal epithelium, hepatocytes, renal proximal tubular cells, adrenal glands, and capillary endothelial cells comprising the blood–brain and blood–testis barrier [18]. Rivaroxaban and apixaban are substrates of both P-gp and another transporter, the Breast Cancer Resistance Protein (BCRP, ABCG2 gene), the latter also involved in the drug intestinal and renal transport. A genome-wide analysis in 2944 patients with AF in the RELY study showed that a single-nucleotide polymorphism (SNP) of the carboxylesterase 1 (CES1rs2244613), present in 32.5% of patients, was associated with reduced transformation of the prodrug dabigatran etexilate into the active metabolite, with the tendency to lower trough levels and lower bleeding risk when compared to non carriers. CES1 SNP rs8192935 was associated with lower peak concentrations, while carriers of SNP rs4148738 of P-gp coding ABCB1 gene had higher peak concentrations [19]. Data on the influence of genetic polymorphisms of the components of drug use cycle are limited for DOACs. Except for dabigatran, no genome-wide association studies have been performed to determine the relevant loci and SNPs and their impact on inter-individual variability for other DOACs in unselected patients in routine clinical practice [20-22].

So far the effect of ABCB1 polymorphism such as rs4148738 has been shown to be relevant only for dabigatran and apixaban in single studies, with an increase and a decrease, respectively of drug levels, albeit without statistically significant or not detected clinically relevant effects [23].

The aim of our study was to determine the inter-individual variability of the anticoagulant effect in subjects taking DOACs for AF or VTE in routine clinical practice and the influence of allele variants of genes coding for transporters such as ABCB1 SNP rs4148738 on DOAC plasma concentration.

MATERIALS AND METHODS

A prospective observational cohort study was performed in consecutive patients with non valvular AF or VTE (either proximal deep vein thrombosis of the lower limbs -DVT- and/or pulmonary embolism-PE). Eligible patients were those taking DOACs (either dabigatran, apixaban, rivaroxaban), according to the registered clinical indications and dosages. Patients were enrolled in our Anticoagulation Clinic from Sept 2013 up to April 2015 within the framework of the START Register (Survey on anTicoagulated pAtients RegisTer) (NCT 02219984). The study was approved by the local Ethics Committee and all enrolled patients provided informed consent to blood sampling and testing.

Inclusion criteria were: age > 18 years, DOAC treatment since at least seven days and not more than 30 days, ability to provide informed consent. Exclusion criteria were: valvular AF, presence of active cancer, DOAC use since more than 30 days, refusal to provide informed consent.

At the time of inclusion after providing informed consent, demographic data were collected on standardized forms in 291 patients: sex, age, weight, BMI, renal function with creatinine clearance determined with the Cockroft-Gault formula, co-morbidities, co-medications, DOAC therapeutic indication, dosage (either 150 or 110 mg b.i.d for dabigatran, either 15 mg b.i.d or o.d or 20 mg od for rivaroxaban, either 5 mg or 2.5 mg b.i.d for apixaban) and treatment duration. Blood samples were then collected by a clean venipuncture into tubes containing 1:9 sodium citrate before (to measure trough levels) and 2-3 hours (to measure peak levels) after DOAC administration.

Blood samples were centrifuged and platelet poor plasma was frozen for the determination of peak and trough levels of DOACs with the diluted thrombin time (dTT) for anti-FIIa activity for dabigatran and the anti-FXa activity for apixaban, rivaroxaban. Anti- Xa activity for apixaban and rivaroxaban was performed with STA Liquid anti-Xa (Stago Diagnostics, Asnières sur Seine, France) and expressed as ng/ml.

Creatinine levels were also determined at 2-3 weeks after starting treatment and creatinine clearance calculated using Cockroft-Gault formula. Whole blood was stored for DNA extraction from peripheral leukocytes for detection of ABCB1 gene rs4148738 polymorphism with real PCR (Anticoagulation Kit 2-RQ, Expert Team Venezia Marghera, Italy) on PCR Real Time System Series 7000 (Applied Biosystems, CA, USA).

Statistical Analysis

No formal sample size calculation was performed as this was a pilot study. Means and medians were

calculated for peak and trough levels for each drug dosage and the coefficient of variation (CV) was also calculated to assess patient inter-individual variability.

The correlation between DOAC levels at peak and trough with continuous variables (age, body weight, creatinine and creatinine clearance) was expressed with Spearman correlation coefficient rho.

The associations of anti-FIIa or anti-FXa activity at peak or trough for each DOAC were tested with univariate analyses with independent continuous variables such as sex, age, BMI, creatinine clearance, and categorical variables such as potentially interfering drugs (PPI and P-gp inhibitors) and the ABCB1 gene (G> A) rs4148738 polymorphism followed by multivariable analysis after correction for drug dosage. A parsimony model with predictors associated with a p-value <0.1 was presented to improve precision and avoid over-fitting.

Statistical significance was associated with a p value <0.05. The data were analyzed using the SPSS statistical package (Version 22.0, SPSS Inc., Chicago, IL).

RESULTS

Table **1** shows the characteristics of the 291 enrolled patients. Patients with VTE (N=101) were younger, more frequently males and had a higher weight and creatinine clearance when compared with patients with AF. Patients with VTE were all taking rivaroxaban 20 mg. Patients taking apixaban for AF had a higher BMI than the other subgroups.

Table **2** shows the mean peak and trough DOAC levels across different groups. A high coefficient of variation was observed in all subgroups, with the lowest for apixaban 2.5mg b.i.d at trough (30%) and the highest for dabigatran 110 mg b.i.d both at trough (62%) and peak (74%).

Table **3** shows the correlation of DOAC peak and trough levels with age, body weight, creatinine, creatinine clearance. Only dabigatran trough levels were directly correlated with age and inversely correlated with creatinine levels. Both peak and trough dabigatran levels were inversely correlated with creatinine clearance.

Table 1: Characteristics of Enrolled Patients

Patients N 291	Atrial Fibrillation				VTE	P*
	Total N 190	Dabigatran N 59	Apixaban N 68	Rivaroxaban N 63	Rivaroxaban N 101	
Age yrs ± SD	76.2±8	74.5 ± 9	73.7 ± 7	78.6 ± 7	58.6 ± 15	0.0001
Weight kg	75.7 ±17	76.3 ± 15	79 ± 19.8	74.1 ± 15.5	83.6 ± 21	0.001
BMI	28.4±2	26.5 ± 4	30.1 ± 8.8	26.3 ± 4.3	32.9 ± 4.4	0.21
Gender M/F (M%)	105/85 (55%)	33/26 (55%)	35/33 (51%)	38/25 (60%)	67/34 (66%)	0.088
Drug daily dose: mg (n)	---	2x150 (26) 2x110 (33)	2x5 (52) 2x2.5 (16)	20 (37) 15 (26)	20	--
Creatinine clearance ml/min	66±26	79.7 ± 24	77 ± 56.3	60.4 ± 18.7	91 ± 39	0.001

*AF patients vs VTE patients.

Table 2: Mean Levels and Coefficient of Variation of DOACS at Peak and Trough

Drug	Dose mg	Trough ng/ml (range)	CV %	Peak ng/ml (range)	CV %
Dabigatran	110	114 (30-324)	62	197 (31-595)	74
Dabigatran	150	91 (45-175)	39	187 (77-427)	44
Apixaban	5	105.1 (32-352)	53	245 (99-486)	34
Apixaban	2.5	70 (22-110)	30	135 (52-200)	50
Rivaroxaban AF	20	35 (14-74)	43	227 (41-449)	50
Rivaroxaban DVT	20	30 (15-76)	40	191 (48-460)	43
Rivaroxaban AF	15	26.8 (15-55)	39	179.6 (77-355)	49

Table 3: Correlation of DOAC Peak and Trough Levels with Age, Body Weight, Creatinine, Creatinine Clearance

	age r*	p	Body weight r*	p	Creatinine r*	p	Creatinine clearance § r*	p
Dabigatran								
Peak	0.13	ns	-0.2	ns	0.2	ns	-0.28	0.041
Trough	0.33	0.016	-0.8	ns	-0.29	0.037	-0.37	0.007
Rivaroxaban								
Peak	0.07	ns	-0.53	0.09	0.40	ns	-0.06	ns
Trough	0.09	ns	0.045	ns	0.12	ns	-0.09	ns
Apixaban								
Peak	0.73	ns	0.07	ns	0.07	ns	0.01	ns
Trough	0.14	ns	-0.03	ns	0.08	ns	-0.01	ns

*Spearman rho; §creatinine clearance calculated with Cockroft-Gault formula.

No correlation of either apixaban or rivaroxaban peak or trough levels was observed with age, body weight or creatinine or creatinine clearance.

Table **4** shows the distribution of ABCB1 rs4148738 polymorphism which was determined only in 142 patients. The minor A allele, either heterozygous or homozygous, was associated with significantly lower peak rivaroxaban levels (p=0.041) when compared with the GG, while no effect was observed on trough levels. A non significant effect of the minor A allele, either heterozygous or homozygous, was observed on both dabigatran peak and through levels. No effect of the minor A allele was observed on either peak or through apixaban levels.

Table **5** shows the multivariate analyses for each DOAC. Dabigatran levels were significantly associated only with creatinine clearance both at peak and trough. Apixaban levels both at peak and trough were significantly dependent only on dosage, with a non significant association with ABCB1 polymorphism. Rivaroxaban levels were significantly associated with dose, age and inversely associated with ABCB1 polymorphism both at peak and trough.

DISCUSSION

The use of DOACs is projected to increase worldwide for treatment and prevention of thromboembolic diseases such as VTE and AF for the increasing aging population. VTE, including DVT and PE, is a common multi-causal thrombotic disease with an annual incidence of 1 per 1,000. PE is associated with a 1-year mortality of 20%, making VTE the third leading cause of cardiovascular death in industrialized countries [24]. AF is the most common arrhythmia with an increasing prevalence with advancing age [25]. Only 1% of patients with AF are younger than 60 years of age, whereas up to 12% of patients are 75 to 84 years of age. Given the increasing prevalence and incidence of AF, this arrhythmia confers a major public health and economic burden on any health care system. The risk

Table 4: Effect of rs4148738 Polymorphism of ABCB1 Gene of P-Glycoprotein on Peak and Trough DOAC Levels

	Dose mg	Pt. N (AA;GA;GG)	Peak mean ng/ml			P*	Trough mean ng/ml			P*
		142 (39;73;30) (21%; 52%;27%)	**AA**	**GA**	**GG**		**AA**	**GA**	**GG**	
DABIG.	150	24 (6,15,3)	179	180	271	ns	85	89	121	ns
APIX.	5	39 (10,18,11)	280	212	248	ns	119	82	104	ns
RIVAX.	20	79 (23,40,16)	140	244	289	**0.041**	33	37	31	ns

*GG+GA alleles vs. AA allele.
MAF: 45.8%; Hardy-Weinberg equilibriium p-value: 0.66.

Table 5: Multivariate Analysis of Factors Associated with Trough and Peak Levels of Different DOACs

	Dabigatran		Apixaban		Rivaroxaban	
	peak	**trough**	**peak**	**trough**	**peak**	**trough**
Age as continuos	ns	ns	ns	ns	β: 0.442 p=0.005	β: 0.52 p=0.003
Sex (M vs F)	ns	ns	ns	ns	ns	ns
Drug Dosage	ns	ns	β: -0.289 p=0.006	β: -0.366 p=0.001	β: -0.789 p=0.001	β: -0.621 p=0.001
BMI	ns	ns	ns	ns	ns	ns
weight	ns	ns	ns	ns	ns	ns
Potentially interfering drugs	ns	ns	ns	ns	ns	ns
Creatinine clearance	β: -0.333 p=0.019	β: -0376 p= 0.017	ns	ns	ns	ns
ABCB1 (AA vs GG+GA)	ns	ns	β: 0.184 p=0.086	ns	β: -0.241 p=0.038	β: -0.266 p=0.039

β: β regression coefficients.

of stroke in AF is reduced by antithrombotic therapy which is however associated with the risk of bleeding.

All major guidelines emphasize the role of oral anticoagulation use for stroke prevention in AF [26]. With the aging population, coordinated efforts will be needed to anticipate the future health care costs related to AF and its impacts on the health care system. This will include appropriate application of antithrombotic therapy according to risk of thromboembolic events and bleeding events [27].

The use of VKAs has been the mainstay of oral anticoagulation for several decades and VKAs have been shown to reduce the risk of systemic embolism in AF by 68-70% and the risk of recurrence in VTE by 90% [1]. VKAs have a narrow therapeutic window and wide inter and intra-individual variability in the anticoagulant effect. As result VKAs require strict laboratory monitoring for dose adjustment with periodic blood sampling to assess their anticoagulant effect. DOACs have been introduced in clinical practice after several clinical trials have shown their non-inferior, and in same instances, their superior efficacy and safety when compared with VKAs such as warfarin, when administered in fixed doses, without the need for laboratory monitoring [26]. In particular all DOACs have shown a reduction by half of the risk of intracranial hemorrhage when compared to warfarin. Treatment with DOACs is less burdensome and simpler for their wider therapeutic window when compared to VKAs. However, when the measurement of DOACs anticoagulant effect in plasma was performed both in healthy volunteers and in patients, a significant inter-individual variability has been found, with an indication that higher or lower blood anticoagulant effects of DOACs can be associated with bleeding and ischemic events [19]. A better knowledge of characteristics and clinical variables such as age, sex renal function, peak and trough DOACs levels and genetic polymorphisms involved in the absorption and elimination of DOACs could facilitate the definition of factors associated with the risk of over- and under-dosage and thus of bleeding and thromboembolic events [27]. Dabigatran, rivaroxaban and apixaban are known P-gp substrates. P-gp activity can be affected by pharmacological inducing or inhibiting agents [28]. This can lead to a significant change in the pharmacokinetics of DOACs, with a decrease or increase (respectively) in the level of intestinal absorption, leading to respectively reduced or increased plasma drug concentrations. In a prospective cohort study of 595 subjects with AF DOAC specific measurements were performed at trough and lower DOAC plasma levels were observed in patients who developed thromboembolic events during 1 year follow-up [29]. Conversely, bleeding complications during DOAC treatment were more frequent among AF patients with higher peak anticoagulant levels [30].

These studies support the concept of measuring DOAC levels at steady state and suggest the need of a more accurate DOAC dose assessment.

Our study confirmed high inter-individual variability for both peak and trough concentrations for all DOACs,

with a trend for a higher CV in peak levels. Only dabigatran peak and trough levels were correlated with creatinine clearance.

We hypothesized that the SNP rs4148738 (intronic region G >A) of ABCB1 gene that codes for P-gp could influence plasma concentrations of dabigatran, rivaroxaban and apixaban, and consequently, impact on the concentration of DOACs.

So far only two ABCB1 gene SNP, rs2032582 and rs1045642, have been evaluated for their potential effect on rivaroxaban plasma levels with indication of impaired drug clearance and suspected GI bleeding [23,31]. In a case series of 10 patients with bleeding complications, all 3 patients with available genotyping data and higher-than-expected rivaroxaban levels were heterozygous or homozygous mutated for the *ABCB1* 1236C > T, 2677G > T, 3435 C > T and rs4148738 single nucleotide polymorphisms [35], while no significant difference was identified in peak steady-state rivaroxaban concentration between mutant haplotypes and wild haplotypes of ABCB1 rs1045642-CYP3A4 rs35599367 and ABCB1 rs4148738 in 79 patients taking rivaroxaban 10 mg after hip and knee replacement surgery [36].

The SNP rs4148738 of ABCB1 gene has been evaluated for its effect on dabigatran [19] and apixaban [33] with a decrease in drug peak concentrations without a clinically relevant effect.

We showed for the first time that rs4148738 polymorphism of ABCB1 gene of P-glycoprotein influenced peak levels of rivaroxaban 20 mg with a significant decrease associated with the minor allele A, while a non significant effect was observed on peak and trough levels of dabigatran 150 mg bid due to the reduced sample size. We could not confirm an effect of rs4148738 polymorphism of ABCB1 on apixaban for the reduced sample size of patients on apixaban.

Limitation of the paper is the lack of data on bleeding and thromboembolic complications during follow-up, however previous studies have shown that such complications might be associated with DOACs levels.

The knowledge of factors associated with variability of DOAC anti-thrombotic effect can allow a better choice of best drug dosage in the individual patient [34]. Not all clinical settings are covered by the factors considered in the major clinical trials of DOACs and improvement in treatment efficacy and safety could be obtained with personalized approach based not only on clinical data but also on integration of pharmacogenetics. Genotyping-derived information may enable clinicians to further tailor the dose of DOACs for individual patients and thereby optimize the balance between efficacy and safety. Further studies are needed to address these issues.

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