Monitoring strategies for patients treated with the new oral anticoagulants and the need for laboratory evaluation of hemostasis

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ABSTRACT

New oral anticoagulants that directly inhibit Factor IIa (dabigatran) or Factor Xa (rivaroxaban, apixaban) are currently available for prevention of venous thromboembolism (VTE) after orthopedic surgery, treatment of acute VTE, and prevention of arterial thromboembolism in non-valvular atrial fibrillation. These agents offer advantages over vitamin K antagonists including rapid onset, shorter half-lives, fewer drug interactions, and the lack of a need for routine monitoring. The fact that monitoring is not required should not, however, lead to lack of surveillance or a *fire and forget medicine* approach because there are several medical conditions that require careful clinical surveillance and, sometimes, laboratory monitoring. The main situations that require close monitoring are major bleeding, assessment of compliance (in particular during comorbidities other than vascular disease, *e.g.* dementia), overdose, sudden or progressive renal dysfunction, extreme body weight, concomitant use of other drugs that may induce impairment of new oral anticoagulants, need for urgent surgery.

Introduction

Goals of antithrombotic treatment with new oral anticoagulants and historical background

The best known and most commonly used anticoagulant drugs include the heparins (unfractionated heparin or low molecular weight heparins or fondaparinux) and vitamin K antagonists (VKAs). Al-

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though the mechanisms of these drugs vary greatly, they do share one common characteristic: they act all as indirect drugs. Vitamin K antagonists act by reducing the synthesis of clotting factors so reducing the power of clotting ability.[1] Heparins act through their link with antithrombin so inducing an increased and fast inhibition of activated clotting factors.[2] The efficacy of these drugs has been shown in various reports over recent years, and also through clinical trials, evidence-based medicine and international guidelines.[3]

Recently, new families of anticoagulant drugs have been developed with different pharmacodynamic and pharmacokinetic profiles. Among these we can distinguish drugs that directly target against Factor Xa or IIa. Of course, direct action toward activated clotting factors are really promising. From this point of view, absorption, metabolism, elimination and interactions with food or other drugs are also different for direct Xa inhibitors and IIa inhibitors if compared with vitamin K antagonists and/or heparins (Table 1).[4] These pharmacological characteristics of new anticoagulants facilitate the daily clinical administration of food or other drugs in the presence of comorbidities, even if clinical experience regarding food interactions is currently limited.

The pharmacological action of classic anticoagulants (*i.e.* vitamin K antagonists and heparins) is monitored through international normalized ratio (INR) values for vitamin K antagonists by aPTT ratio for unfractionated heparins and by levels of inactivated Xa factor for low molecular weight heparins/fondaparinux, while such monitoring is usually not required for new oral anticoagulants, such as direct Xa in-

hibitors (*i.e.* rivaroxaban, apixaban, edoxaban and others) or IIa inhibitors (*i.e.* dabigatran) based also on a relatively short half-life.

However, *not monitoring* should mean do not monitor prothrombin time (PT)-INR or aPTT, but it does not mean do not oversee the situation or *fire and forget medicine*! This concept should always be kept in mind in new approaches to anticoagulant treatments to ensure a correct strategy is adopted concerning thrombotic disease, patients and drugs. Moreover, in this field, several trials study the safety and efficacy of treatment with new oral anticoagulants for prevention of cardioembolic stroke in patients with atrial fibrillation or for prevention and treatment of venous thromboembolism. However, the anticoagulant activity of new oral anticoagulants can be monitored in rare cases by several laboratory tests, even if these have not been standardized or are not routinely available.

Clinical conditions with indication to monitor new oral anticoagulants

Prescription of this new class of drugs requires vigilance, also because this is a fragile patient population and new oral anticoagulants (NOACs) are drugs with potentially severe complications. Patients should return on a regular basis for ongoing review of their treatment, preferably every three months. This may be carried out by general practitioners with experience in this field and/or by appropriate secondary care physicians.

Renal function, a predictor of bleeding with anticoagulant drugs in general, should be assessed prior to initiation of therapy with novel oral anticoagulants and monitored during treatment, much more frequently than in patients with chronic renal dysfunction. Monitoring is particularly important for dabigatran, which is excreted by the kidneys.[5]

In accordance with recent EHRA2013 guidelines,[6] monitoring should be performed according to this scheme:
- Yearly: hemoglobin, renal and liver function
- 6-monthly: renal function if creatinine clearance (preferably measured by the Cockroft method) 30-60 mL/min, or if on dabigatran and >75 years or fragile
- 3-monthly: if creatinine clearance 15-30 mL/min
- on indication: if intercurring condition that may impact renal or hepatic function.

Because their direct antithrombotic activity is due to their pharmacodynamic profile, routine monitoring of new oral anticoagulants is not indicated either for IIa inhibitor or for Xa inhibitors. Moreover, the rate of complications in reported studies was very low for all drugs so routine monitoring of new oral anticoagulants is not indicated from a clinical point of view.

Therefore, clinical conditions in which new oral anticoagulants are monitored are similar to those clinical conditions that also indicate monitoring of the classic anticoagulants (*i.e.* anti-vitamin K drugs and heparins), such as when a severe life-threatening complication is present or possible. Clinical conditions in which monitoring of new oral anticoagulants is suggested may be summarized as follows: major bleeding (in particular, sudden bleeding or major bleeding with recent intake of new oral anticoagulants), thrombotic events, assessment of compliance (*i.e.* in particular, during comorbidities other than vascular disease, *e.g.* dementia), overdose, sudden or progressive renal dysfunction, extreme body weight, concomitant use of other drugs that may induce impairment of new oral anticoagulants, need for urgent surgery.[7]

So, principally, monitoring of new oral anticoagulants is a clinical monitoring, with particular attention to the conditions listed above.

However, specific monitoring of anticoagulant activity of new oral anticoagulants may be required for patients with sudden kidney failure or with progressive renal dysfunction with creatinine clearance less than 20 mL, particularly in conjunction with a surgical approach.

Major bleeding is always a life-threatening disease or complication, and monitoring the anticoagulant activity of any anticoagulant drug may help clinical management, even though a specific antidote is not available, and often it may not be required to restore blood flow or to escape further bleeding complications.

Emergency situations (*e.g.* hemorrhage, overdose, urgent surgery/invasive procedure) necessitate rapid assessment of coagulation status. This clinical approach may be helpful both for sudden bleeding and for recent drug intake or over dosage, or for patients at risk of bleeding who are non-compliant. On the other hand, patients with extreme body weight and patients who are taking several drugs may have a different distribution of new oral anticoagulants, in particular Xa inhibitors, respectively for different metabolic response and pharmacokinetic and/or pharmacodynamic interactions (Tables 1 and 2).[4,8] Modest changes in the use of IIa inhibitors are needed for extreme body weight; however, caution is needed in cases of low body mass index, especially if associated to renal impairment.

However, conventional coagulation assays have limitations when used to measure novel oral anticoagulant effect. There is, in fact, no precise relationship between the routine coagulation tests available and the anticoagulant activity (Table 3).[9]

Pharmacological basis of reduced monitoring of new anticoagulants

Xa inhibitors

Rivaroxaban, apixaban and edoxaban are direct, reversible, competitive inhibitors of free Xa factor. Rivaroxaban has a half-life of 5-9 h, while apixaban has a

Table 1. Food and drugs that may alter pharmacological actions of new oral anticoagulants.

	Food interactions	Metabolism	Drug interactions	Population at risk	Special populations
Dabigatran	Pharmacokinetic effect: - t_{max} delayed - C_{max} and AUC unchanged - Reduced inter-individual variability	85% renal elimination 6% fecal elimination Metabolized by esterase-catalysed hydrolysis in plasma or liver and P-gp transporter mechanisms	CYP3A4 and P-gp inhibitors: - clarythromycin P-gp inhibitors: - quinidine, amiodarone, verapamil CYP3A4 and P-gp inducers: - rifampicin, St John's Wort, pantoprazole NSAIDs: - aspirin, naproxen, diclofenac Antiplatelet agents: - clopdogrel, etc.	Cardiac arrhythmia Minor depression Bacterial infections (including pharyngitis, tonsillitis, MRSA, TB, Meningococcus) Malaria Cluster headaches GERD Cardiovascular disease Pain, fever and inflammation, including arthritis	Elderly people Liver disease Renal impairment
Rivaroxaban	Pharmacokinetic effect: - t_{max} increased - C_{max} and AUC unchanged - Reduced inter-individual variability Pharmacodynamic effect: - Increased maximum PT prolongation - Time to maximum PT delayed	33% renal elimination of unchanged drug 33% renal elimination of drug metabolites 33% fecal elimination Metabolized by: CYP3A4, CYP2J2 and CYP450-indipendent mechanism, and P.gp transporter mechanism in kidney/intestine	CYP3A4 and P-gp inhibitors: - ketoconazole, itraconazole, voriconazole, posaconazole,ritonavir, clarithromycin CYP3A4 and P-gp inducers: - rifampicin, St John's Wort, phenytoin, carbamazepine, phenobarbitone NSAIDs: - aspirin, naproxen, Antiplatelet agents: clopdogrel, etc.	HIV and AIDS Minor depression Fungal infections Bacterial infections (including pharyngitis, tonsillitis, MRSA, TB, *Meningococcus*) Respiratory tract infections Cardiovascular disease Epilepsy and bipolar disorder Pain, fever and inflammation, including arthritis	Elderly people Liver disease Renal impairment
Apixaban	Pharmacokinetic effect not reported	46% fecal elimination 25-28% renal elimination metabolized by: CYP3A4, mechanism in liver, and multiple other pathways, in kidney/intestine	Antiplatelet agents: clopdogrel, etc.	Cardiovascular disease	Not reported

Adapted from Walenga and Adiguzel, 2010.[4]

Table 2. Summary of potential metabolic drug interactions with new oral anticoagulants.

Dabigatran Etexilate	Rivaroxaban	Apixaban
Inhibitors of P-gp: Verapamil: reduce dose Dronedarone: avoid	Potent inhibitors of Cyt P3A4 and P-gp:* avoid	Potent inhibitors of Cyt P3A4 and P-gp:* avoid
Potent inducers of P-gp,° avoid	Potent inducers of CytP3A4# and P-gp:° use with caution	Potent inducers of CytP3A4# and P-gp:° use with caution

*, Potent inhibitors of CYP3A4. Antifungals: ketoconazole, itraconazole, voriconazole, posaconazole. Protease inhibitors: ritonavir, atazanavir. chloramphenicol, clarithromycin; °, Potent P-gp inducers: rifampicin, St. John's Wort, phenytoin, carbamazepine; #Potent CYP3A4 inducers: rifampicin, St. John's Wort, phenytoin, carbamazepine, phenobarbital, Cyop cytochrome P450 isoenzyme; F factor, P-gp P-glycoprotein; CYP3A4 and P-gp inhibitors, clarithromycin; P-gp inhibitors, quinidine, amiodarone, verapamil. *Adapted from Huber* et al., 2013.[8]

Table 3. Effect of new oral anticoagulants on commonly used coagulation tests.

	Prothrombin time (PT)	Activated partial thromboplastin time (PTT)	Thrombin clotting time (CTT)	Ecarin clotting time (ECT)	Hemoclot assay	Anti-Factor Xa activity	
						Clot based	chromogenic
Dabigatran	↑or no change (low sensitivity, varies with reagents)	↑(varies with reagents)	↑	↑	↑	↑	ND
Rivaroxaban	↑or no change (not sensitive at low concentrations, varies with reagents	↑or no change (less sensitive than PT)	–	–	–	↑	↑(sensitive and specific when calibration curve used)
Apixaban	↑or no change (other tests more sensitive, may vary with reagents)	↑or no change (other tests more sensitive, may vary with reagents)					

ND, not detected. *Adapted from Siegal and Crowther, 2013.*[9]

half-life of 8-11 h. Peak plasma concentrations are similar for both and are reached in approximately 2-4 h. Rivaroxaban and apixaban are mainly metabolized by the liver, in particular by the CYP3A4 system. Studies have reported the efficacy and safety of rivaroxaban for treatment of venous thromboembolism (the EINSTEIN DVT, EINSTEIN PE and EINSTEIN EXTENSION studies[10-12]) and several doses were used at start of treatment and in long-term treatment of VTE (15 mg twice daily for 3 weeks followed by 20 mg once daily).

Double blind randomized trials for treatment of VTE are ongoing also for apixaban (AMPLIFY) and edoxaban (HOKUSAI) but results are not yet available.

Clotting tests to monitor Xa inhibitors

Although in daily clinical management, and based on their pharmacokinetic and pharmacodynamic profiles, specific or periodic monitoring of anticoagulant activity of new oral anticoagulants is not required, we reported a series of conditions in which anticoagulant activity of new oral anticoagulants is needed and may be helpful in clinical decision making. Several tests are available for rigorous monitoring of intensity of anticoagulant activity of new oral anticoagulants with direct action toward Factor Xa. However, coagulation tests may often have a different sensitivity depending on the blood concentration of Xa inhibitors.

A PT with a plain thromboplastin can be used to determine the relative intensity of anticoagulation due to rivaroxaban (*e.g.* in an emergency or in an urgent clinical scenario as reported above). On the other hand, each laboratory should be aware of the sensitivity of their PT assay to new oral anticoagulants that are direct inhibitors of Factor Xa, and this can be

achieved using commercially available direct Xa-inhibitors plasma calibrants (*e.g.* rivaroxaban).[13,14]

Several global conventional clotting tests, as well as clotting or chromogenic assays to measure anti-Factor Xa activity, have been studied. Anti-Factor Xa assays (without exogenous antithrombin) and specific PT assays can be used with rivaroxaban plasma calibrants to determine the drug level. The chromogenic tests found a dose-dependent relationship between anti-Factor Xa activity and rivaroxaban concentration. Modified specific Factor Xa chromogenic assays should be investigated in more depth.

A dependent prolongation of PT, dilute PT, and aPTT was observed with rivaroxaban. Results may vary depending on the reagents used and this variation cannot be standardized with the INR system commonly used for vitamin K antagonists. So, results of the PT-test can be expressed in plasma concentrations of rivaroxaban rather than PT seconds or ratio, after which a standard calibration curve can be made. PT was assessed by mixing 50 μL of plasma poor platelets at 37°C with 100 μL of calcium thromboplastin. Several different thromboplastins were tested and reagents from brain rabbit (such as Neoplastin and Neoplastin plus) seem to have a better impact than recombinant human thromboplastin or thromboplastin from placenta. These tests often required special conditions, such as dilute prothrombin time, because in normal PT for common assays and measurements a high concentration of thromboplastin is used (*i.e.* more thromboplastin is used in routine PT tests than in physiological conditions).

Also rivaroxaban was seen to influence aPTT but the effect was weak. This was to be expected since there is a trend for direct FXa inhibitors to have a

greater effect on PT than on aPTT. Yet a prolongation of aPTT may be found in particular when the test is performed with kaolin.

IIa inhibitors

Dabigatran, the main IIa inhibitor, acts by binding to the catalytic site of thrombin. Dabigatran etexilate is its pro-drug and this is available for therapeutic and commercial use. It requires ester cleavage after absorption to be transformed into active form. Its half-life is nearly 12-17 h after administration of several doses. Dabigatran is then mainly eliminated by kidney (80%) and the remaining fractions by liver. The RE-COVER, RE-COVER II, RE-MEDY, RE-SONATE[15-18] studies reported the efficacy and safety of dabigatran for treatment of venous thromboembolism; doses used were 150 mg twice daily.

Clotting tests to monitor IIa inhibitors

Periodic monitoring of the anticoagulant activity of new oral anticoagulants is also not required for dabigatran. However, when clinical conditions are critical and coagulation tests are required, there are several tests that evaluate the effect of dabigatran. Coagulation tests behave differently with increasing concentration of dabigatran. Of course, the maximum effect of dabigatran on clotting parameters occurs at the same time as maximal plasma concentrations, indicating that thrombin inhibition by dabigatran is a direct effect linked to the central plasma compartment.[19]

Various coagulation assay tests behave differently with increasing concentrations of dabigatran, such as the time curves for activated partial thromboplastin time (aPTT), prothrombin time (PT, expressed as international normalized ratio, INR), thrombin clotting time (TT), ecarin clotting time (ECT). Thrombin inhibitor assay (HEMOCLOT) values parallel the plasma concentration-time curve of dabigatran.[20] Of course, when we interpret a coagulation assay, it is essential to know when dabigatran etexilate was administered relative to the time of blood sampling.

The aPTT assay targets the intrinsic pathway of the coagulation cascade. Prolongation of the aPTT occurs with increasing dabigatran plasma concentration although the aPTT concentration-response curve is curvilinear and flattens at higher concentrations (≥ 200 ng/mL). Furthermore, when given to healthy volunteers in supra-therapeutic doses (400 mg three times daily), aPTT ratios were mostly in the range of 2-3 at trough and peak dabigatran plasma concentrations (>400-500 ng/mL).

The PT assay represents the clotting time in the extrinsic coagulation pathway. Dabigatran has little effect on the PT (INR) at clinically relevant plasma concentrations. Therapeutic concentrations of dabigatran usually result in only modest elevations of INR,

while INR rises by 2.0 at supra-therapeutic concentrations of dabigatran.

The TT assay directly assesses the activity of thrombin in a plasma sample and, therefore, directly measures dabigatran activity. The TT is particularly sensitive to the effects of dabigatran and displays a linear dose-response ratio over different therapeutic concentrations. The TT test is readily available in most hospitals.

The ECT assay is a specific assay for thrombin generation. The activator of the assay, ecarin, is a snake venom that specifically activates prothrombin resulting in the generation of meizothrombin, an unstable precursor of thrombin. As DTIs are able to inhibit the thrombin-like activity of meizothrombin, the ECT test provides a direct measure of dabigatran activity.

The Hemoclot® Thrombin Inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) is a sensitive diluted TT assay which allows quantitative measurement of DTI activity in plasma, based on inhibition of a constant and defined concentration of thrombin. Mixing normal pooled human plasma and diluted test plasma (clotting is initiated by adding a constant amount of highly purified human alpha-thrombin), we obtain a linear relationship between dabigatran concentration and clotting time (from approx. 30-75 s).[21]

Conclusions

The new oral anticoagulants have shown considerable promise in large-scale, randomized clinical studies for the management of thromboembolic disorders, and have been approved for clinical use in specific indications. These agents offer advantages over VKAs, including rapid onset, shorter half-lives, fewer drug interactions, and lack of need for routine monitoring. However, it is very important to remember that the use of anticoagulant drugs should be carefully monitored clinically, especially in populations at particular risk.

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