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.

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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.

| Drug          | Pharmacokinetic effect:                                                                 | Metabolism                                      | Drug interactions                                                                 | Population at risk         | Special populations   |
|---------------|----------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------|-----------------------|
| Dabigatran    | Pharmacokinetic effect:                                                                 | Metabolism                                      | CYP3A4 and P-gp inhibitors:                                                        | Cardiac arrhythmia          | Elderly people        |
|               | - t\(_{max}\) delayed                                                                | 85% renal elimination                           | - clarythromycin                                                                  | Minor depression            | Liver disease         |
|               | - C\(_{max}\) and AUC unchanged                                                      | 6% fecal elimination                            | P-gp inhibitors:                                                                  | Bacterial infections        | Renal impairment      |
|               | - Reduced inter-individual variability                                                | Metabolized by esterase-catalysed hydrolysis in | - quinidine, amiodarone, verapamil                                               | (including pharyngitis,     |                       |
|               |                                                                                        | plasma or liver and P-gp transporter mechanisms | CYP3A4 and P-gp inducers:                                                         | tonsillitis, MRSA, TB,     |                       |
|               |                                                                                        |                                                 | - rifampicin, St John’s Wort, pantothenol                                         | Meningococcus)             |                       |
|               |                                                                                        |                                                 | NSAIDs:                                                                          |                             |                       |
| Rivaroxaban   | Pharmacokinetic effect:                                                                 | 33% renal elimination of unchanged drug        | CYP3A4 and P-gp inhibitors:                                                        | HIV and AIDS                | Elderly people        |
|               | - t\(_{max}\) increased                                                                | 33% renal elimination of drug metabolites      | - ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, clarithromycin | Minor depression            | Liver disease         |
|               | - C\(_{max}\) and AUC unchanged                                                      | Metabolized by: CYP3A4, CYP2J2 and CYP450-      | CYP3A4 and P-gp inducers:                                                         | Fungal infections           | Renal impairment      |
|               | - Reduced inter-individual variability                                                | independent mechanism, and Pgp transporter     | - rifampicin, St John’s Wort, phenytoin, carbamazepine, phenobarbital              | Bacterial infections        |                       |
|               |                                                                                        | mechanism in kidney/intestine                  | NSAIDs:                                                                          | (including pharyngitis,     |                       |
|               |                                                                                        |                                                 | - aspirin, naproxen, diclofenac                                                  | tonsillitis, MRSA, TB,     |                       |
|               |                                                                                        |                                                 | Antiplatelet agents:                                                             | Meningococcus)             |                       |
|               |                                                                                        |                                                 | - clopidogrel, etc.                                                              |                             |                       |
| Apixaban      | Pharmacokinetic effect:                                                                 | 46% fecal elimination                           | Antiplatelet agents:                                                             | Cardiovascular disease      | Not reported          |
|               | not reported                                                                            | 25-28% renal elimination of unchanged drug     | clopidogrel, etc.                                                                |                             |                       |
|               |                                                                                        | Metabolized by: CYP3A4, mechanism in liver, and | Antiplatelet agents:                                                             |                             |                       |
|               |                                                                                        | multiple other pathways, in kidney/intestine   | clopidogrel, etc.                                                                |                             |                       |

Adapted from Walenga and Adiguzel, 2010.

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

| Drug          | Inhibitors of P-gp: Verapamil: reduce dose | Potent inhibitors of Cyt P3A4 and P-gp: avoid | Potent inhibitors of Cyt P3A4 and P-gp: avoid |
|---------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|
| Dabigatran    | Dronedarone: avoid                         | Potent inducers of Cyt P3A4 and P-gp: avoid  | Potent inhibitors of Cyt P3A4 and P-gp: avoid |
| Rivaroxaban   | Potent inducers of P-gp: avoid             |                                             |                                             |
| Apixaban      |                                             |                                             |                                             |

*, 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, Cytochrome P450 isoenzyme. F factor, P-gp glycoprotein, CYP3A4 and P-gp inhibitors, clarithromycin, P-gp inhibitors, quinidine, amiodarone, venlafaxine. Adapted from Huber et al., 2013.
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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 studies10-12) 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

| 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** |
| **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

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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-SONATE15-18 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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