SEED Coagulation

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The new oral anticoagulant drugs – what influence do they have on routine coagulation testing?

The need for anticoagulant therapy

The fundamental principle of haemostasis is to minimise blood loss at sites of vessel injury whilst maintaining blood flow at all times. This is maintained via a highly regulated fine-tuned interaction of multiple biological processes. When this balance is disturbed in favour of excessive clot formation, patients are at risk of developing pathological thrombosis which will interfere with blood circulation and may be fatal. Such patients are commonly treated with anticoagulant drugs which aim to restore the haemostatic balance and therefore minimise the risk of thrombosis. Examples of disorders for which oral anticoagulants are commonly prescribed are venous thromboembolism (deep vein thrombosis/pulmonary embolism), atrial fibrillation, coronary heart disease and ischaemic stroke.

Warfarin

The most commonly prescribed anticoagulant for long term use is warfarin. The great advantage of warfarin is that it is an oral drug. The disadvantage however is that there is substantial variability in its biological effects from person to person and also in a single individual over time. There are multiple factors that contribute to this including genetics, diet and concomitant drug use. As the benefits of warfarin are restricted to a narrow therapeutic window, periodic dose adjustments are required to ensure that patients remain within the target INR range. Laboratory monitoring is therefore mandatory in order to balance the risk of a recurrent event due to ongoing hypercoagulabilty versus the risk of bleeding complications. The long term use of these agents is thus complicated for the doctor and burdensome for the patient, requiring significant patient commitment for maximal benefit.

Heparin

Unfractionated heparin (UFH) has been widely used for the initial treatment of patients with thrombosis because it has a very rapid onset of action, in contrast to warfarin which takes a couple of days for the full anticoagulant effect to manifest. Although the action of UFH is rapid in onset the degree of anticoagulation is however not predictable. This is partly due to the fact that heparin binds non-specifically to various plasma proteins. Protein bound heparin is unable to participate in the anticoagulant action. This is particularly noticeable in the acute stages of illness due to the increase in so called acute phase proteins. Because of this patients on heparin need to undergo regular monitoring to ensure that the level of anticoagulation is within the therapeutic range. Excess heparin places the patient at risk of bleeding and too little would exacerbate the already existing prothrombotic condition. These limitations led to the development of low molecular weight heparins (LMWH) which have a more predictable action, did not require regular laboratory monitoring and have fewer bleeding complications. Whilst LMWHs have substantially improved anticoagulant care, they like UFH, have to be given by injection and therefore are unsuitable for long-term anticoagulation, which is what is needed for the majority of patients. Furthermore, UFH, and to a lesser extent LMWH place patients at risk of developing heparin induced thrombocytopenia necessitating serial platelet count monitoring in those at risk.

New oral anticoagulants

Heparin and warfarin have been extensively used over the past 50 years. However the highly variable dose responses and need for close laboratory monitoring, has driven the

search for alternate anticoagulant drugs with more predictable effects eliminating the need for laboratory monitoring and frequent individual patient dosage adjustments. In contrast to warfarin and heparin which render their anticoagulant effect by targeting multiple points within the coagulation pathway, the hallmark of the newer drugs is targeted blockade of a specific activated coagulation factor thus achieving a predictable response. Additionally, the focus of development of the new drugs is oral administration as this is an absolute requirement for these drugs to be considered a suitable replacement for warfarin for long-term use. The characteristics of the ideal anticoagulant are shown in Tab. 1.

Oral administration
Single daily dose
Predictable dose response and pharmacokinetics
Low rate of bleeding events
No routine laboratory monitoring required (coagulation tests or platelet counts)
Wide therapeutic window
No dose adjustment required
Little interaction with food or drugs
Low or absent non-specific plasma protein binding
Inhibition of both free and clot-bound activated coagulation factors
Readily reversible in the event of an overdose

Tab. 1 *Characteristics of the ideal anticoagulant*

Several new oral anticoagulant drugs have been developed with better efficacy and an enhanced safety profile, which are closer to the ideal anticoagulant. New oral anticoagulant drugs that are currently available on the market fall into two broad categories – those that produce a direct, selective and reversible inhibition of factor Xa and those that target factor IIa. Compared to warfarin they have the following advantages: oral administration with predictable pharmacokinetics and dose response, wide therapeutic window, shorter half-life, little interaction with food and other drugs, rapid onset of action and no need for routine laboratory monitoring.

As more evidence emerges from clinical trials, so the number of clinical applications for which these new drugs are licensed for use expand. The earliest approvals were for short term thromboprophylaxis after hip and knee surgery followed by long-term use for stroke prevention in atrial fibrillation and treatment of venous thromboembolism. It should be noted that approval varies from country to country. The two most widely used drugs are rivaroxaban and dabigatran.

Rivaroxaban

Rivaroxaban is an oral direct FXa inhibitor produced by Bayer Healthcare and marketed in several countries under the trade name Xarelto. The drug reaches its peak level about 2 – 4 hours after ingestion. The half-life is about 5 – 9 hours. Approximately two thirds of the drug is metabolized with half of this then being eliminated via the kidneys and the other half via the faecal route. The remaining third is excreted unchanged in the urine. It is not necessary to adjust the dose in renal failure. It is contraindicated in patients with hepatic disease associated coagulopathy who have a bleeding risk and should be used with caution in patients with moderate hepatic impairment. It is not recommended for use in patients being treated with HIV protease inhibitors. Rivaroxaban is given at a fixed dose and does not require routine laboratory monitoring.

Dabigatran

Dabigatran etexilate is a direct oral thrombin inhibitor produced by Boehringer Ingelheim and marketed under the trade name Pradaxa. It is a prodrug that undergoes transformation in the liver to the active drug, dabigatran. The half-life is 14 – 17 hours. About 80 % of the drug is excreted unchanged by the kidneys and 20 % by the biliary system after undergoing conjugation. Dabigatran is therefore contraindicated in patients with severe renal function impairment (creatinine clearance <30 mL/min) with a dose reduction being required for creatinine clearance between 30 and 50 mL/min. Dabigatran is given at a fixed dose and does not require routine laboratory monitoring.

Why do we need to know about the new oral anticoagulant drugs?

Whilst there is abundant evidence from clinical trials that anticoagulation with these new drugs is safely achieved without laboratory monitoring, there are nevertheless clinical situations where knowledge of the effect of these drugs on coagulation testing is essential. Even though laboratory monitoring is not required to specifically determine the dosage of dabigatran or rivaroxaban required for

an individual patient, being anticoagulants, they do affect coagulation testing. In order not to make any erroneous interpretations, it is important to know how routine coagulation tests are affected as patients undergoing coagulation screening, for whatever reason, may be taking these drugs. As more clinical conditions are added to the approved indications for use of these new drugs, so the patient base taking these drugs grows. Consequently, even if these drugs may not be approved for use in a particular country, in the era of global travel, the likelihood that a traveler seeking medical care in a foreign country may be taking them, must always be considered.

Furthermore, situations may arise where urgent assessment of the degree of anticoagulation may be required (Tab. 2).

When a patient is bleeding
When a patient has taken an overdose
When a patient has a thrombosis on treatment – here one would need to determine if this is due to treatment failure or poor patient compliance
When a patient has developed renal failure
When a patient has taken the drug in the last 24 hours and urgent surgery or an invasive procedure is necessary

Tab. 2 *Clinical scenarios that may require urgent assessment of degree of anticoagulation with the new oral anticoagulant drugs*

For most clinical situations, the availability of qualitative information is enough to manage the clinical situations described in Tab. 2. The main concern here would be very high levels (bleeding risk) or very low levels (thrombosis risk). As the pharmacokinetics of these drugs is predictable, it is important to know the time elapsed between blood collection and the last dose of drug taken by the patient.

The effect of the new anticoagulant drugs on coagulation tests

Thrombin and FXa are the key enzymes for clotting therefore all assays where thrombin or FXa is generated are potentially affected by the oral direct thrombin inhibitor dabigatran and the oral direct factor Xa inhibitor rivaroxaban. Assays affected are all global screening assays, single factor assays and many speciality assays. Immunoassays (such as D-dimers) and von Willebrand factor activity assays are unaffected.

The challenge in providing definitive information about how these drugs interfere with coagulation testing is that the degree of impact is dependent on the type of drug, the test method, the make of commercial reagent. Some but not all effects are predictable. Thrombophilia testing is particularly vulnerable to interference but this is beyond the scope of this edition.

1. Prothrombin Time (PT)

a. Rivaroxaban

The PT is prolonged in the presence of rivaroxaban. The observed effect is however highly variable amongst different thromboplastin reagents. Innovin (Siemens Healthcare) has been shown to be the least responsive with Recombiplastin (Instrumentation Laboratories) being the most responsive. The reason for this is that thromboplastin reagents have varying sensitivities (i.e. different ISI values) to anticoagulant agents, including those that directly inhibit factor Xa. Some studies have shown an up to three-fold difference in PT ratio (patient plasma PT in seconds divided by control plasma PT in seconds) using different PT reagents. Innovin is relatively unresponsive to rivaroxaban. In contrast to the vitamin K antagonists such as warfarin, conversion of the PT value to an INR does not eliminate this extreme variability. There is however a direct relationship between the dose of drug and PT prolongation although this is not sensitive enough to ascertain the concentration of drug present. If a patient taking rivaroxaban has a normal PT, this generally implies that the degree of anticoagulation is subtherapeutic. This should however not be interpreted as meaning that a patient with a normal PT does not have some degree of anticoagulation, although this would generally be no more than would be achieved through a prophylactic dose of LMWH. Please note that only PT (reported in seconds) and not the INR can provide some guidance on the determination of presence or absence of rivaroxaban induced anticoagulation.

b. Dabigatran

In contrast to rivaroxaban, the PT is relatively insensitive to dabigatran but this too is variable for different thromboplastin reagents.

2. Activated Partial Thromboplastin Time (APTT)

a. Rivaroxaban

The APTT shows a curvilinear response to rivaroxaban but is less sensitive to low drug concentrations than dabigatran. APTT results are influenced by the type of analyser and reagent used e.g. some may show no prolongation of APTT clotting time even at peak drug levels, whereas others may still be subtherapeutic despite high APTT results. In this regard, the PT is a better indicator than the APTT to assess the intensity of anticoagulation.

b. Dabigatran

The APTT is sensitive to dabigatran showing a curvilinear dose response with a sharp increase at low concentrations and then a more linear response at higher levels and then flattening out at doses greater than 200 ng/mL. Although there is variation amongst different analysers and reagents, the degree of variability is far less than observed for rivaroxaban with results being within ± 10 % of a reference method. As a rule, high APTT results are indicative of supratherapeutic levels and a normal APTT ratio (the patient value in relation to the control value) is likely to indicate a subtherapeutic level. The same caveat (as mentioned for rivaroxaban and PT) applies, namely that a normal APTT does not necessarily exclude the patient from having some degree of anticoagulation, although this would generally be no more than would be achieved through a prophylactic dose of LMWH.

3. Thrombin Time (TT)

a. Rivaroxaban

This has no effect on the TT.

b. Dabigatran

Dabigatran being a direct thrombin inhibitor affects the TT. The TT shows a linear dose response although most commercially available TT assays will be too sensitive to provide any quantitative information. A normal TT would exclude the presence of dabigatran whereas a markedly prolonged or unclottable TT cannot differentiate between subtherapeutic, therapeutic or supratherapeutic levels.

4. Fibrinogen

The impact of the new oral anticoagulants on clot-based fibrinogen tests is variable.

a. Rivaroxaban

Very high doses of rivaroxaban cause an unexplained slight reduction in some assays.

b. Dabigatran

Dabigatran will cause a concentration dependent effect on giving false low fibrinogen results in methods using relatively low concentrations of fibrinogen. High thrombin concentration assays have minimal or no effect.

A summary of the impact of these drugs on routine coagulation tests is shown in Tab. 3.

	Direct Factor Xa Inhibitor (Rivaroxaban)	Direct Thrombin Inhibitor (Dabigatran)
PT (in sec) and INR	↑ to ↑↑	↑
APTT	↑	↑ to ↑↑
Thrombin Time	None	↑↑
Clauss fibrinogen	None	None /slight ↓
Multifibrin U fibrinogen	None	↓↓
Derived fibrinogen	None /slight ↓	None /slight ↓
D-dimer	None	None

Tab. 3 *Impact of rivaroxaban and dabigatran on routine coagulation tests*

The laboratory assessment of the direct oral anticoagulants

Even though rivaroxaban and dabigatran do not require routine laboratory monitoring, in specific patients and under certain clinical circumstances (Tab. 2) it will be necessary to get some objective indication of the anticoagulant effect of these drugs by means of laboratory measurement. The results of the latter investigation are not intended to be used to adjust drug dosage but to assess if the patient is under- or over-anticoagulated.

Whilst specific assays for the assessment of anticoagulant activity induced by rivaroxaban (Biophen® DIXaI) and dabigatran (Hemoclot Thrombin Inhibitor) are commercially available from Hyphen, these are not routinely available even in countries where these drugs are being prescribed with increasing frequency. Consequently it would be important to know which of the routinely available coagulation assays are best suited to at least provide a semi-quantitative assessment of direct oral anticoagulant drug induced anticoagulation in an emergency situation.

a. Rivaroxaban

In the absence of a specific anti-factor Xa activity assay, the PT is the test of choice for the assessment of rivaroxaban anticoagulant effect. A plasma concentration of 200 µg/L, which is expected after a once daily dose of 10 mg should prolong the PT by about 1.5 times. As mentioned previously, it must be noted that different thromboplastins show great variability in this effect.

b. Dabigatran

In the absence of a specific direct thrombin inhibitor assay, the best routine test to use to assess dabigatran anticoagulant activity is the APTT. The prolongation of clotting time is dose dependent with a plasma concentration of 200 µg/L resulting in an APTT value of about 2.5 times the baseline value. The only downside is that the dose response is not linear.

Unlike the APTT, the thrombin time has a linear dose dependent relationship to dabigatran. Whilst the standard TT test is much too sensitive to be useful in assessing anticoagulant effect, modification by using diluted plasma samples makes this a useful and readily accessible assay.

Conclusions

Whilst the new oral anticoagulant drugs do not require laboratory monitoring to inform drug dosing decisions, it is important that clinicians and laboratory personnel alike are aware of the influence that they have on routine coagulation assays. This is imperative to avoid erroneous interpretation of these baseline tests. Furthermore, it is essential that the laboratory is equipped to provide the clinician with at least qualitative guidance on the degree of anticoagulation attributable to these drugs in selected situations (as listed in Tab. 2).

Take home message

- As a rule the new oral anticoagulant drugs do not need routine laboratory monitoring, however there is still a need for laboratory testing to assess the degree of over- or under-anticoagulation in certain clinical circumstances.
- Both rivaroxaban and dabigatran affect routine clot-based coagulation assays the extent of which is highly variable by test as well as reagent used.
- Whilst the routine assays (PT, APTT and TT) are not suitable for quantitative assessment of drug level, the PT can be used to provide qualitative judgement of degree of anticoagulation by rivaroxaban and the APTT (and modified TT) can be used for dabigratran.

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