Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity

Joanne van Ryn[1]; Joachim Stangier[2]; Sebastian Haertter[2]; Karl-Heinz Liesenfeld[2]; Wolfgang Wienen[3]; Martin Feuring[4]; Andreas Clemens[4]

[1]Department of Drug Discovery Support, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [2]Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [3]Department of Pulmonary Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany; [4]Department of Medical Affairs, Boehringer Ingelheim GmbH, Ingelheim, Germany

Summary

Dabigatran etexilate is an oral, reversible direct thrombin inhibitor that is approved in the EU and several other countries for the prevention of venous thromboembolism after elective hip and knee replacement, and is in advanced clinical development for other thromboembolic disorders. Dabigatran has a predictable pharmacokinetic profile, allowing for a fixed-dose regimen without the need for routine coagulation monitoring. In certain clinical situations such as serious bleeding into critical organs (e.g. intracerebral bleeding), potential overdose and emergency surgery, clinicians will need to make an assessment of the anticoagulant status of a patient receiving dabigatran before deciding on future management strategies. If available, thrombin clotting time (TT), ecarin clotting time (ECT) and TT determined by Hemoclot® thrombin inhibitor assay are sensitive tests to evaluate the anticoagulant effects of dabigatran. Prothrombin time (INR) is less sensitive than other assays and cannot be recommended. The activated partial thromboplastin time (aPTT) can provide a useful qualitative assessment of anticoagulant activity but is less sensitive at supratherapeutic dabigatran levels. There are limited data for activated clotting time (ACT). Overall, the aPTT and TT are the most accessible qualitative methods for determining the presence or absence of anticoagulant effect. Although there is no specific antidote to antagonise the anticoagulant effect of dabigatran, due to its short duration of effect drug discontinuation is usually sufficient to reverse any excessive anticoagulant activity. In case of potential overdose, the feasibility of early administration of activated charcoal and subsequent charcoal filtration are undergoing preclinical evaluation. Dabigatran can also be dialysed in patients with renal impairment. In instances of life-threatening bleeding, where conventional measures have failed or are unavailable, other non-specific prohaemostatic agents such as recombinant activated factor VII and prothrombin complex concentrates can be considered.

Keywords

Dabigatran etexilate, dabigatran, direct thrombin inhibitor, coagulation assays, reversal

Correspondence to:
Dr. Joanne van Ryn
Department of Drug Discovery Support
Boehringer Ingelheim Pharma GmbH & Co. KG
Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany
Tel.: + 49 7351 547774, Fax: + 49 7351 837774
E-mail: Joanne.vanRyn@boehringer-ingelheim.com

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Introduction

Dabigatran etexilate is the prodrug of dabigatran, a potent, non-peptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule (1–3). Oral administration of dabigatran etexilate produces a predictable pharmaco-dynamic effect. Consequently, dabigatran etexilate has been clinically developed in various indications using fixed-dosing without the need for routine coagulation monitoring or dose adjustment. Currently, dabigatran etexilate has been approved in the EU and several other countries for prophylaxis of thromboembolism in patients undergoing total knee or hip replacement. A recent trial has also shown that dabigatran etexilate significantly reduces stroke risk with a better safety profile compared with warfarin in patients with atrial fibrillation (AF) (4). Other indications under investigation include the treatment of venous thromboembolism (VTE) (5) and treatment of thromboembolic complications following acute coronary syndromes (6). In all indications, fixed-dose regimens of dabigatran etexilate have provided effective anticoagulation with a favourable bleeding profile.

While coagulation monitoring is not required with dabigatran etexilate in routine clinical practice, effects on various coagulation assays have been studied. These data may be relevant in certain

clinical situations, such as serious bleeding into critical organs (e.g. intracerebral bleeding), potential overdose and emergency surgery, where clinicians (especially those in emergency departments) will need to make an assessment of the anticoagulant status of a patient receiving dabigatran before deciding on future management strategies. The aim of this review is to summarise the effects of dabigatran on different coagulation assays and provide potential guidance in the management of anticoagulant effects in certain situations.

Pharmacokinetic profile of dabigatran etexilate and dabigatran

Following oral administration, dabigatran etexilate is rapidly hydrolysed *in vivo* to the active form, dabigatran (7). The onset of effect of dabigatran starts immediately after dosing with peak plasma concentrations and maximal anticoagulant effects achieved within 2–3 hours (h). Studies in patients undergoing hip replacement surgery or stroke prevention in AF show a close correlation between plasma dabigatran concentration and the degree of anticoagulant effect (8, 9). ▶Table 1 shows the expected peak and trough dabigatran plasma concentrations at steady state following administration of 220 mg once daily (od) and 150 mg twice daily (bid) based on a population pharmacokinetic model derived from patients with AF enrolled in the dose-ranging PETRO (Prevention of Embolic and ThROmbotic events) trial (10) (data on file).

Dabigatran etexilate is given od in patients undergoing elective total hip or knee replacement, and bid for secondary prophylaxis for the treatment of VTE or stroke prevention in AF. The drug is predominantly excreted unchanged via the kidneys (~80%) with the remainder eliminated via the bile (7). Patients with a moderate (creatinine clearance [CL_{CR}] <50 ml/minute [min]) or severe (CL_{CR} <30 ml/min) decline in renal function may exhibit prolonged excretion rates and elevated plasma concentrations of dabigatran (11). Dabigatran is contraindicated in patients with severe renal dysfunction (CL_{CR} < 30 ml/min) and will accumulate in patients with renal failure (12).

Dabigatran and dabigatran etexilate are neither metabolised by nor induce or inhibit cytochrome P450 drug metabolizing enzymes. In addition, dabigatran displays low (35%) plasma protein binding, implying that displacement interactions are unlikely to affect its pharmacokinetics and pharmacodynamics (7). Food prolongs the time to peak plasma dabigatran levels by approximately 2 h without significantly influencing overall exposure (13). Thus, the predictable pharmacokinetic profile of dabigatran supports a fixed-dose regimen without the need for routine coagulation monitoring.

Effect of dabigatran on coagulation assays

The effect of dabigatran on the various coagulation assays has been investigated *in vitro* by the addition of defined concentrations of dabigatran to plasma from healthy human volunteers (2), as well as *ex vivo* using plasma samples from both healthy volunteers and patients (8, 14, 15). As dabigatran acts on thrombin-mediated conversion of fibrinogen to fibrin, it has an effect on all of the routine coagulation assays.

The various coagulation assay tests behave differently with increasing concentrations of dabigatran (▶Fig. 1) (13). The time curves for activated partial thromboplastin time (aPTT), prothrombin time (PT, expressed as international normalised ratio [INR]), thrombin clotting time (TT) and ecarin clotting time (ECT) values parallel the plasma concentration–time curve of dabigatran (▶Fig. 2) (14, 16). 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. Further details of the effects of dabigatran on the different coagulation assays are summarised below.

When interpreting a coagulation assay it is essential to know when dabigatran etexilate was administered relative to the time of blood sampling. For example, coagulation assay results obtained in a blood sample taken 2 h after dosing with dabigatran etexilate differ from those obtained in samples taken 8 or 12 h after the same dose (Fig. 2). In contrast, the timing of blood sampling to drug administration is not so relevant for warfarin because of the prolonged activity of the coagulation factors arising from its long half-life (days).

Activated partial thromboplastin time (aPTT)

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) (Fig. 1). When given to healthy volunteers in supratherapeutic 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) (14). In patients receiving

Table 1: Peak and trough dabigatran plasma concentration at steady state following administration of 220 mg od[a] and 150 mg bid[b] in a population pharmacokinetic model of patients with AF enrolled in the PETRO trial (data on file).

Dose and regimen	$C_{max,\ ss}$ (ng/ml)	$C_{trough,\ ss}$ (ng/ml)
220 mg od	183 (62–447)	37 (10–96)[c]
150 mg bid	184 (64–443)	90 (31–225)[d]

Data expressed as median (5th and 95th percentiles), modelled on the PETRO study with a median creatinine clearance of 75 ml/min. [a]Dose approved for the prevention of thromboembolism after hip and knee replacement surgery. [b]Dose tested in RE-LY trial for the prevention of stroke in patients with atrial fibrillation (4). [c]$C_{trough,ss}$ measured at 24 hours. [d]$C_{trough,\ ss}$ measured at 12 hours. $C_{max,ss}$ = steady-state maximum dabigatran plasma concentration. $C_{trough,ss}$ = steady-state trough dabigatran concentration. od = once daily. bid = twice daily.

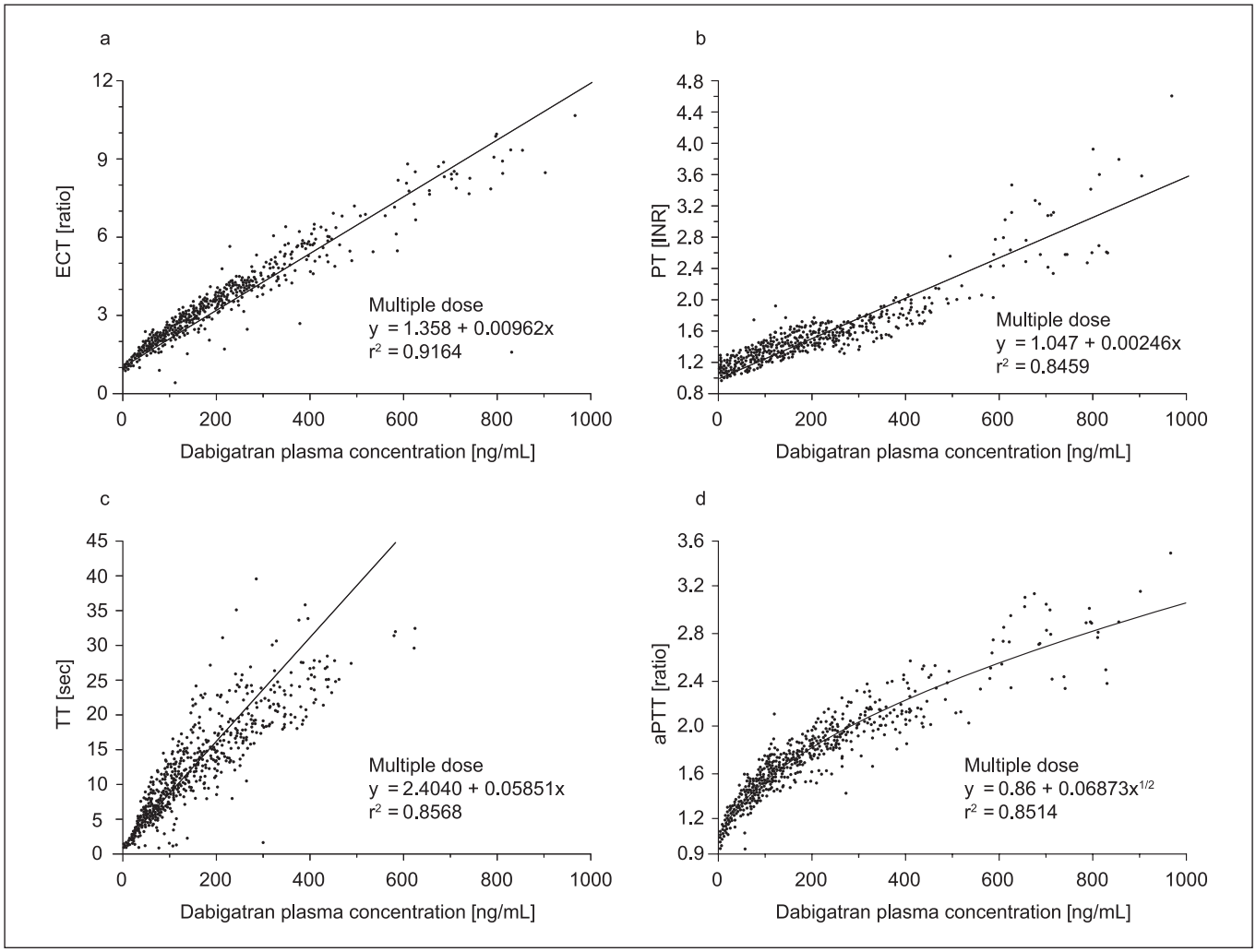

Figure 1: Prolongation of a) ECT, b) PT (INR), c) TT and d) aPTT vs. dabigatran plasma concentration at steady state after multiple doses of dabigatran etexilate (14). The TT exceeded the upper limit of the coagulation measurement time at higher concentrations of dabigatran.

chronic therapy with dabigatran 150 mg bid, the median peak aPTT is approximately two-fold that of control. Twelve hours after the last dose (trough level), the median aPTT is 1.5-fold that of control, with less than 10% of patients exhibiting two-fold increases in aPTT (greater than 65 seconds) (▶Fig. 3) (9). Thus, the aPTT is relatively insensitive within the range of plasma concentrations of dabigatran likely to be observed in patients.

Measurement of aPTT can vary according to the type of coagulometer and sensitivity of the reagents used. To evaluate the potential impact of these variables, cross-validation of aPTT measured in 58 local and two core laboratories (using various reagents and coagulometers) participating in the PETRO (Prevention of Embolic and ThROmbotic events) trial versus a central laboratory was performed (17). Good agreement in aPTT was observed after spiking pooled plasma with dabigatran (600 ng/ml), with values obtained in most local laboratories within 10% and almost always within 20% of values obtained by the central laboratory (▶Fig. 4). However, while aPTT measurement may provide a qualitative indication of the anticoagulant activity of dabigatran, as with other direct thrombin inhibitors (DTIs) (18), it is not suitable for precise quantification of anticoagulant effect especially at high plasma concentrations of dabigatran (15). Very high aPTT values should be repeated or confirmed via another test, such as ECT or dilute TT (Hemoclot®). Despite these limitations, aPTT can be useful in determining an excess of anticoagulant activity although changes in aPTT during monitoring treatment should be interpreted with caution.

Prothrombin time (PT) and international normalised ratio (INR)

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 (14). At recommended pro-

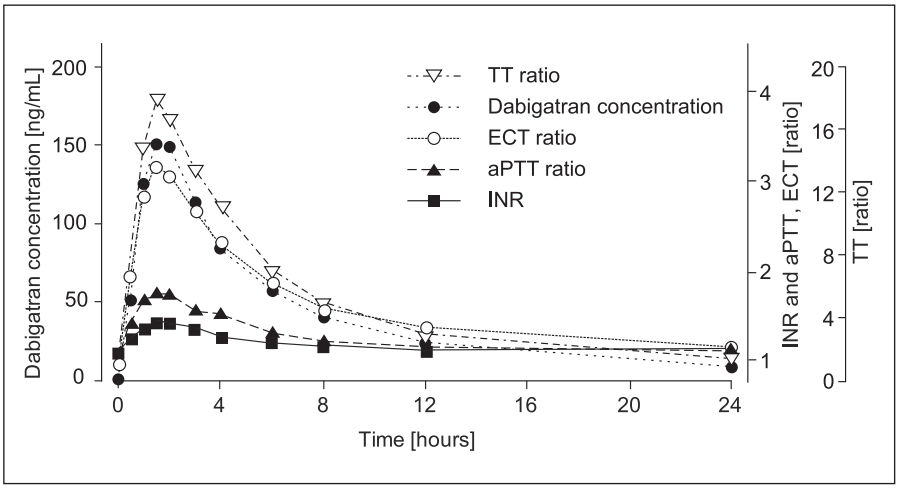

Figure 2: Geometric mean plots of aPTT prolongation, INR, TT and ECT together with plasma concentrations of dabigatran vs. time following a single dose oral dose of 200 mg dabigatran etexilate (N = 6) (14).

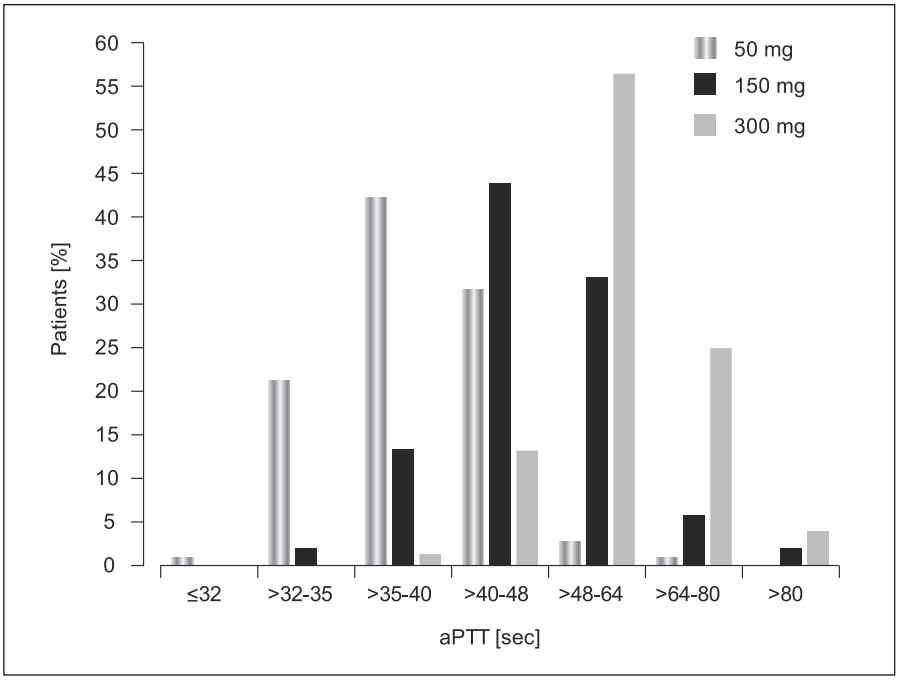

Figure 3: Distribution of patients (number [%]) according to mean trough aPTT after oral administration of 50, 150 and 300 mg dabigatran etexilate twice daily (10, 54).

phylactic doses of dabigatran etexilate following orthopaedic surgery (220 mg od), the INR is relatively insensitive to the activity of dabigatran and is therefore unsuitable as a primary measure of anticoagulant activity (19). Therapeutic concentrations of dabigatran usually result in only modest elevations of INR (INR 2.0 at supra-therapeutic concentrations of dabigatran) (Fig. 1).

Thrombin clotting time (TT)

The TT assay directly assesses the activity of thrombin in a plasma sample and therefore provides a direct measure of the activity of DTIs. TT tests are readily available in many hospital laboratories.

The TT is particularly sensitive to the effects of dabigatran, and displays a linear dose-response over therapeutic concentrations (Fig. 1). In healthy volunteers, steady state levels after administration of dabigatran 100 mg three times daily resulted in a TT ratio of 14 times baseline (14). While cut-off limits can be defined for well standardised and calibrated tests, this is not possible for local measurement of TT because the reagents in different laboratories are not standardised. At dabigatran concentrations greater than 600 ng/ml the test frequently exceeds the maximum measurement time of coagulometers (data on file) suggesting that this method may be too sensitive for emergency monitoring. The TT assay is most useful as a sensitive method for determining if any dabigatran is present. Changes in monitoring treatment of dabigatran should also be interpreted with caution.

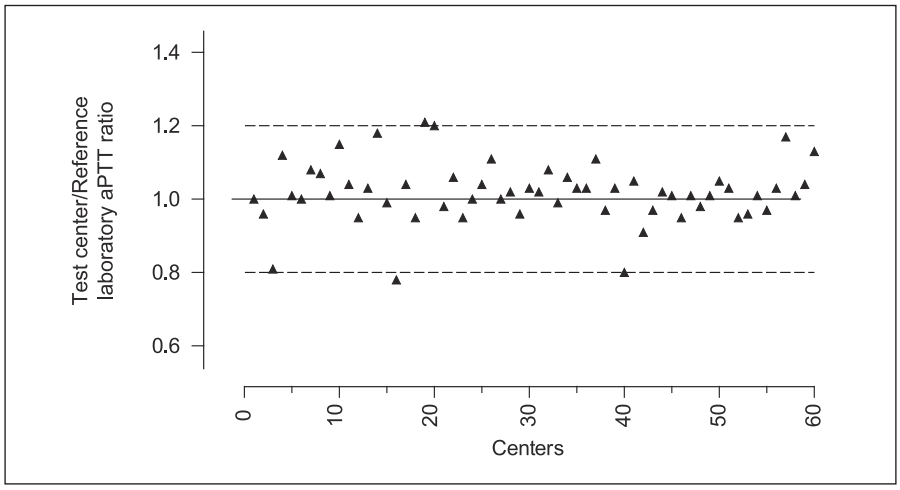

Figure 4: Variation in aPTT levels across local centers participating in PETRO trial compared with central reference laboratory (17). Each data point represents mean of nine plasma pooled samples spiked with 600 ng/ml of dabigatran. At each center, three measurements were performed each day on three different days for each plasma sample. The local centre/reference laboratory ratios were between 0.95 and 1.05 at 41 sites, within the range of 0.95 and 0.80 at four sites, between 1.05 and 1.20 at 13 sites, and 0.78 and 1.21 at one site each.

Activated clotting time (ACT)

The ACT is a quantitative assay based on a similar test principle to the aPTT, except that clotting is initiated in whole blood samples using a contact activator without the addition of phospholipids and calcium. It is most frequently used as a bedside assay to measure the anticoagulant effect of unfractionated heparin in patients undergoing percutaneous coronary intervention or coronary artery bypass surgery. There are limited data for ACT with dabigatran. I*n vitro* studies using human whole blood and a portable coagulometer (Hemochron®; Keller Medical GmbH, Bad Soden, Germany) showed a concentration-dependent increase in ACT which was linear with dabigatran concentrations up to 250 ng/ml but then flattened at higher concentrations (≥500 ng/ml) (data on file) (▶Fig. 5). The concentration of dabigatran required to double the ACT was around 200 ng/ml. The effects of dabigatran on the ACT were similar to those for aPTT and consistent with findings observed with the DTI melagatran, the active compound of oral ximelagatran (20). No systematic investigation of the use of ACT has been performed in patients. Thus, while measurement of ACT or aPTT could be used in particular clinical situations, the rather flat dose-response curve limits the utility of this assay.

Hemoclot® Thrombin Inhibitor assay

The Hemoclot® Thrombin Inhibitor assay (Hyphen BioMed, Neuville-sur-Oise, France) is a sensitive diluted TT assay which allows for quantitative measurement of DTI activity in plasma, based on inhibition of a constant and defined concentration of thrombin. Diluted test plasma (1:8 to 1:20) is mixed with normal pooled human plasma, and clotting is then initiated by adding a constant amount of highly purified human α-thrombin. There is a direct

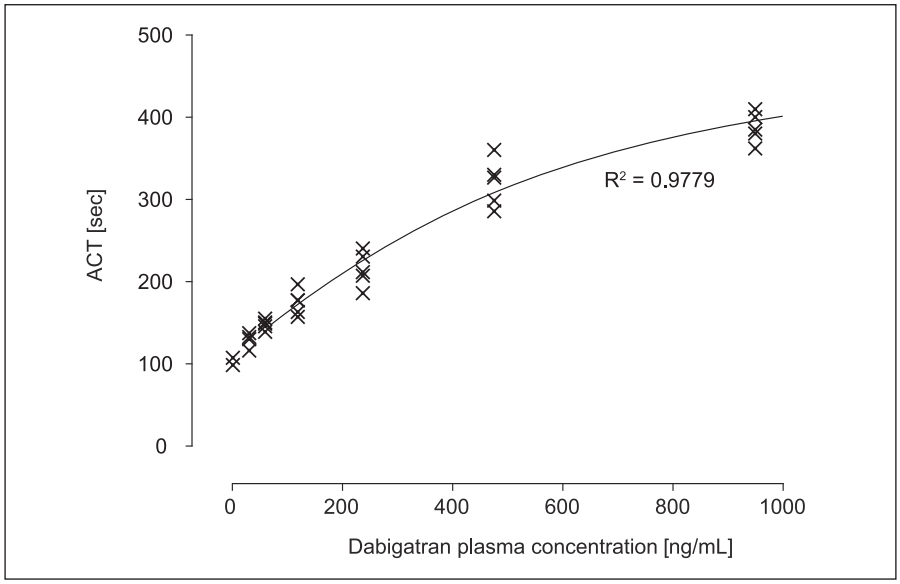

Figure 5: The relationship between ACT and plasma concentration of dabigatran in human whole blood *in vitro* (data on file). Results based on *in vitro* results of five volunteers. Individual responses and the mean plot are shown. R^2 is the coefficient of determination for the linear least-squares regression of ACT vs. plasma dabigatran concentration.

linear relationship between dabigatran concentration and clotting time (from about 30 to 75 seconds) (▶Fig. 6) (21). The assay has no matrix effect and can be used for any of the available DTIs, including dabigatran.

Although external calibration of the Hemoclot® assay with hirudin enables determination of dabigatran concentrations expressed as 'hirudin equivalents' (22), direct calibration with stable, lyophilised dabigatran standards is more precise. Clinical studies indicate that the assay with dabigatran calibrators can be used to measure dabigatran levels in children (23). The specific assay for measurement of dabigatran plasma levels remains in clinical development and is not yet commercially available.

Ecarin clotting time (ECT)

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 the activity of DTIs (24).

Studies in healthy volunteers and patients show close linear correlation between ECT prolongation and plasma concentrations of DTIs, including melagatran, the active metabolite of ximelagatran, and dabigatran (9, 16, 18). ECT ratios of 2–4 have been observed after administration of dabigatran etexilate 150 mg bid (9). Clinical experience supports the ECT as a sensitive test for measuring anticoagulant activity in orthopaedic patients and during cardiopulmonary by-pass surgery, with superiority over the aPTT (24). To date, the ECT has been largely used as a research tool with somewhat limited access. While development of commercial kits may improve the practicality of this test (24), these kits have not been standardised or validated with dabigatran. For these reasons, ECT cannot be recommended for emergency monitoring of anticoagulant effects.

Coagulation assay measurement in patients undergoing surgery

Analysis of data from patients undergoing elective hip replacement surgery shows that there is greater test variability with the aPTT and ECT when dabigatran etexilate is initiated within 1–4 h after surgery than later (8). While the mechanism underlying this response immediately after surgery remains unclear, perioperative effects, such as the transfusion of large volumes of fluids and/or perioperative bleeding, may contribute. Concomitant medication (such as diuretics, drugs accelerating gastrointestinal transit time, paracetamol [acetaminophen] and CYP3A4 inhibitors), patient demographics and standard clinical laboratory parameters have no relevant effects on any of the aPTT and ECT model parameters in this population. Thus, aPTT and ECT levels measured in the first 2–3 days following surgery should be interpreted with caution.

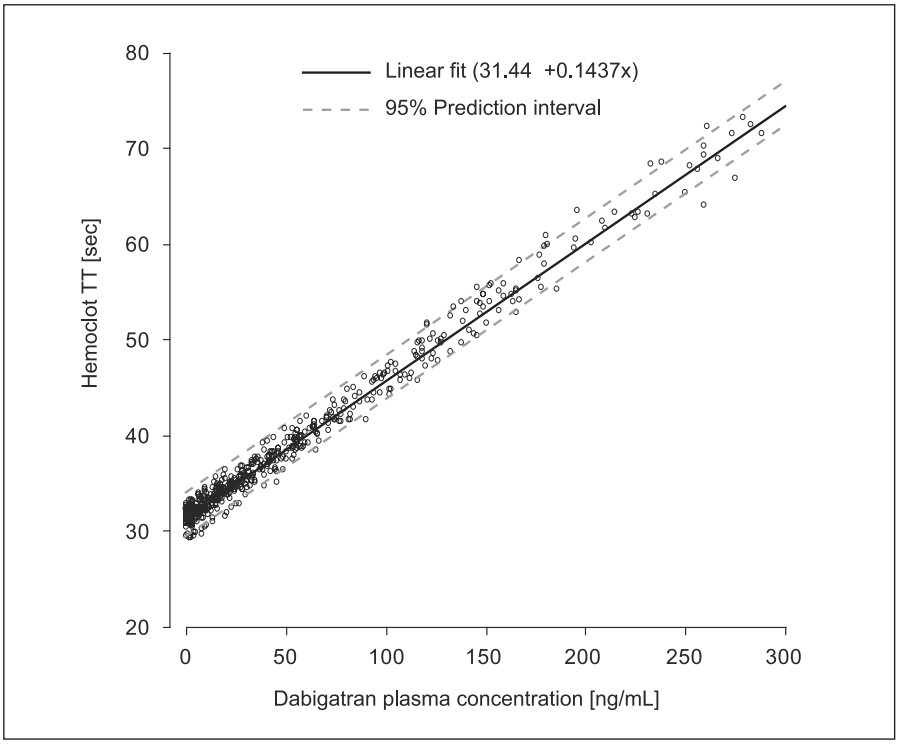

Figure 6: Linear relationship between Hemoclot® TT assay and dabigatran concentrations in samples from healthy volunteer subjects receiving dabigatran etexilate 220 mg (21).

Reversing the anticoagulant effect of dabigatran

Anticoagulation always carries a risk of bleeding, either due to dosing errors, haemorrhagic diatheses or emergency medical procedures. Bleeding is the major adverse reaction of anticoagulants and is associated with significant morbidity and long-term adverse outcomes, including increased mortality (25–27). In rapidly progressing haemostatic emergencies, such as pericardial, intraspinal or intracranial bleeds, the anticoagulant effects of heparins and vitamin K antagonists (VKA) can be reversed with protamine sulfate and prothrombin supplementation, respectively (28). The administration of protamine sulphate is not without risk due to the potential for allergic response with ensuing hypotension and bronchoconstriction (29). Additionally, the use of parenteral or oral vitamin K to counteract the effect of VKA is not immediate, with intravenous administration taking at least 12 h to completely normalise the INR (30). Although several newer anticoagulants, including the factor X inhibitors (e.g. fondaparinux, rivaroxaban and apixaban) and the DTIs (e.g. argatroban, bivalirudin, ximelagatran/melagatran and dabigatran) have a shorter duration of anticoagulant effect than VKA, they do not as yet have established specific antidotes (31). Specific situations in which the anticoagulant effect of dabigatran may wish to be reversed are discussed in more detail below.

In patients undergoing elective surgery

Patients with therapeutic levels of dabigatran etexilate who undergo elective surgery or invasive procedures are at increased risk for bleeding. Therefore, surgical interventions may require the temporary discontinuation of dabigatran etexilate. Dabigatran etexilate should be discontinued at least 24 h prior to elective surgery depending on the degree of renal impairment and risk of bleeding. Since patients with renal impairment may exhibit elevated concentrations of dabigatran, it may be beneficial to check serum creatinine several days prior to elective surgery and calculate the CL_{CR}. In patients with normal renal function and a standard bleeding risk, discontinuation of dabigatran 24 h before surgery will decrease plasma levels to approximately 25% of steady-state trough levels, reducing to approximately 12–15% of trough levels 36 h before surgery and approximately 5–10% two days (48 h) before surgery. In patients at higher risk of bleeding or in major surgery where complete haemostasis may be required dabigatran etexilate should be stopped 2–4 days before surgery. ▶Table 2 provides guidance for discontinuation of dabigatran etexilate prior to elective surgery according to the risk of bleeding and degree of renal impairment.

For patients at high risk of bleeding, where possible a TT should be performed 6–12 h before surgery and a normal result, as defined by the local laboratory, should be obtained. Persistent prolongation of the TT in the absence of heparin, other DTIs (e.g. lepirudin and bivalirudin), fibrin/fibrinogen degradation products or high concentrations of serum proteins (e.g. myeloma) represents strong evidence of elevated levels of dabigatran in the blood. Surgery should be delayed in patients at high risk of bleeding with an elevated TT. Since patients with renal impairment may exhibit elevated concentrations of dabigatran, serum creatinine may be checked when the patient has prolonged TT values persisting beyond the expected clearance time.

Patients with severe renal impairment (CL_{CR} < 30 ml/min) should have dabigatran permanently discontinued unless their renal function improves. In addition, patients with severe renal impairment should have a delay in surgery, if at all possible, and/or haemodialysis or other measures should be considered prior to surgery as their risk of bleeding will be elevated. If the TT test is not available the aPTT, although less precise, can be used. In the post-procedural period dabigatran treatment can be reinitiated as soon as clinically indicated. If oral medication is not feasible, parenteral heparinisation should be considered.

Renal function (CL_{CR}, ml/min)	Half-life (hours)[a]	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding[b]
> 80	13 (11–22)	24 hours	2–4 days
> 50 to ≤ 80	15 (12–34)	24 hours	2–4 days
> 30 to ≤ 50	18 (13–23)	at least 2 days (48 hours)	4 days
≤ 30[c]	27 (22–35)	2–5 days	> 5 days

[a]Data from renal impairment study in healthy volunteers (11), geometric mean (range). [b]Types of surgery associated with a high risk of bleeding (or in major surgery where complete hemostasis may be required) include but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (e.g. major cardiac, respiratory or liver disease) and concomitant use of antiplatelet therapy. [c]Dabigatran etexilate is contraindicated for use in these patients. CL_{CR} = creatinine clearance.

Table 2: Guide to the discontinuation of dabigatran etexilate before elective surgery in patients receiving once or twice-daily dosing with a standard or high risk of bleeding.

In the case of potential dabigatran overdose

Since dabigatran etexilate is a lipophilic molecule (log P=3.8) adsorption by activated charcoal is expected. The use of activated charcoal to reduce absorption and avoid intoxication following potential overdose of dabigatran etexilate has been investigated *in vitro* using two models (32). In the first study, binding of dabigatran etexilate to activated charcoal in water was used to simulate recent ingestion (2–3 h) of large amounts of dabigatran etexilate in the stomach fluid. Activated charcoal suspension (Ultracarbon®, Merck, Whitehouse Station, NJ, USA) containing 12.5 g of activated charcoal was added to the contents of 5, 10 and 20 capsules of dabigatran etexilate 150 mg suspended in 100 ml of water (pH 2.4–2.7). Following filtration, concentrations of dabigatran etexilate could not be detected in any of the three charcoal-treated suspensions, indicating that more than 99.99% of dabigatran etexilate was adsorbed by the activated charcoal. In the second study, binding of dabigatran to activated charcoal in plasma was used to simulate situations where dabigatran was absorbed after ingestion and was present in high concentrations in the plasma. Dabigatran was added to a human plasma pool at concentrations of 470 and 940 ng/ml. The sample was then split, with active charcoal added to one-half at the manufacturer's specified concentration (125 mg/ml) or a 1:11 dilution of this in the other half. Addition of activated charcoal at both concentrations reduced levels of dabigatran to <1.01 ng/ml which was close to or below the lower limit of quantification of the assay.

These preliminary *in vitro* data indicate that dabigatran etexilate can be successfully adsorbed by classical activated charcoal therapy. However, this has not been tested *in vivo* or in patients. Additionally, drug disposition is a very important consideration which has not been adequately controlled for in these *in vitro* studies. Because of this, it is advised that charcoal should be given within 1–2 h of overdose before dabigatran etexilate is absorbed within the intestine. Further removal of dabigatran from plasma via haemoperfusion over a charcoal filter is under evaluation although additional clinically relevant models are required before this can be recommended in patients. Further information on the use of haemodialysis is discussed below.

In case of severe or life-threatening bleeding

In clinical trials, the risk of bleeding with dabigatran was generally comparable with that observed for existing anticoagulants. Pooled data from phase III studies involving 8,135 patients undergoing total hip or knee replacement showed that major bleeding occurred in 1.4% and 1.4% of patients treated with a short 1–5 week course of dabigatran 220 mg od or enoxaparin, respectively (33). Patients receiving concomitant non-steroidal anti-inflammatory drugs (half-life ≤ 12 h) and aspirin (< 160 mg/day) had a similar risk of major bleeding as those receiving dabigatran etexilate alone (34). Additionally, in a trial of 18,113 patients with AF receiving fixed doses of dabigatran etexilate with and without aspirin (< 100 mg/day), the major bleeding risk associated with a dose of 150 mg bid was comparable with that observed with warfarin (3.1% per year vs. 3.4% per year, p=0.31), and significantly lower with a dose of 110 mg bid (2.7% per year, p=0.003) (4). However, for both doses of dabigatran, the incidence of intracranial bleeding was significantly lower than with warfarin (4).

In the phase II dose-finding trial in stroke prevention in AF patients (PETRO) the additional use of aspirin (81 or 325 mg) resulted in a higher number of total bleeding events (major or minor) in each of the dabigatran groups (50-, 150-, or 300-mg dabigatran bid) (10). In the highest dose (300 mg bid), total bleeding events were significantly higher in the group receiving aspirin compared with the group without concomitant aspirin (p=0.0003). Therefore, as with all anticoagulant drugs (35), the concomitant use of antiplatelet therapy (aspirin ± thienopyridine) may have consequences on the bleeding risk and also needs to be considered in the emergency assessment of a patient's situation and prognosis.

In the event of bleeding complications in patients receiving dabigatran etexilate, management should be individualised according to the severity and location of the haemorrhage (▶Fig. 7). Treatment should be discontinued and the source of bleeding investigated. As dabigatran predominantly undergoes renal excretion, an adequate diuresis must be maintained. Supportive strategies to control severe bleeding include delayed administration of the next dose or discontinuation of dabigatran etexilate therapy, mechanical compression, surgical haemostasis and transfusion of blood-products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy). In patients with normal renal function, plasma concentration levels decline relatively quickly following discontinuation. Given adequate renal function, within 12 h of a 150 mg dose of dabigatran etexilate, steady-state plasma concentrations of dabigatran are <100 ng/ml and aPTT is about 1.5 times baseline (15). If all of the above measures fail to control bleeding, the use of haemodialysis or administration of specific reversal agents may be considered.

Specific agents for the reversal of anticoagulant effects of dabigatran

Concern regarding potential overdosing or uncontrolled bleeding has prompted testing of agents known to reverse haemostatic defects and enhance wound-localised thrombin generation. At present, there are no published clinical data on the use of these agents in patients receiving dabigatran etexilate and limited information on other new oral anticoagulants (36). Thus, their use in treating anticoagulant-associated bleeding is generally based on a combination of pre-clinical data, anecdotal case reports and the absence of alternative therapies that might be effective (37).

Recombinant activated factor VII

Recombinant activated factor VII (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is an approved potent procoagulant and general haemostatic agent that can initiate haemostasis at sites of bleeding by directly activating thrombin on the surface of platelets in the absence of tissue factor (38). As a result, it has been proposed that this agent may have potential in reversing the effects of a variety of anticoagulants, including the new oral thrombin inhibitors. It has been successfully used "off-label" in patients with refractory life-threatening haemorrhage (39).

Healthy volunteer and *ex vivo* data suggest that rFVIIa antagonises the anticoagulant effect of a variety of agents (40, 41), including dabigatran. In a rat tail model of template bleeding, addition of rVIIa (0.1 or 0.5 mg/kg) significantly reduced bleeding time (BT) and prolongation of aPTT associated with high dose dabigatran (1 µmol/kg bolus + 0.5 µmol/kg/h infusion for 25 min) in a dose-dependent manner (42). Recombinant VIIa at 0.5 mg/kg reduced BT from 11.6-fold (ratio to control) to 1.1-fold and aPTT prolongation by dabigatran and from 8.3-fold to 3.8-fold.

There have, however, been inconsistent findings relating to the use of rFVIIa with other DTIs. In one study in healthy volunteers, a single dose of rFVIIa (90 mg/kg) did not reverse the anticoagulant effect associated with high concentrations of melagatran, the active compound of ximelagatran (43). In contrast, in another healthy volunteer study which used inhibition of thrombin generation in shed blood as an index of activity, rFVIIa reversed the anticoagulant effect of melagatran (44). This may in part be due to the volume of distribution of melagatran, which is larger (30–40 l) than just the central compartment. Lipophilic ximelagatran is sequestered in cells after absorption, and slowly converted to melagatran, which resulted in a longer half-life for melagatran. Thus, several doses of rFVIIa may be required. Further case reports indicate that the use of rFVIIa can reverse the anticoagulant effects of the DTIs lepirudin and bivalirudin when used in place of heparin in patients undergoing cardiopulmonary bypass surgery (45, 46). Thus, the utility of rFVIIa in patients who are actively bleeding has not been firmly established (37).

Prothrombin complex concentrates (non-activated and activated)

Prothrombin complex concentrates (PCCs) contain all of the vitamin K-dependent coagulation factors and have therefore been useful for the rapid reversal of coagulopathy by replacing vitamin K-dependent clotting factors and restoring normal haemostasis in the context of over-anticoagulation induced by VKA (47). Several non-activated PCCs are approved for use, each effective in shortening the time to INR correction with a low risk of thrombotic adverse events (47). They can be divided into those that are: "4-factor-concentrates" containing adequate amounts of vitamin K-dependent factors II, VII, IX and X (e.g. Beriplex®, Octaplex®, Proplex T®) or "3-factor-concentrates" containing significantly lower amounts of factor VII (less than one third of factor IX) (e.g. Prothrombinex-HT®, Profilnine® and Bebulin®)(31, 48). Following on from their successful use in patients with haemophilia A, activated PCCs (APCC) have also found a role as a general haemostatic agent outside of the setting of VKA reversal in patients with clinically significant bleeding events. Feiba VH® (Factor Eight Inhibitor By-passing Activity, Vapor Heated; Baxter, Vienna, Austria) is an APCC that contains vitamin-K dependent coagulation factors II, IX, X and protein C mainly in non-activated forms and factor VII mainly in the activated form. APCC preparations have been reported to have thrombogenic potential; therefore, as in all emerg-

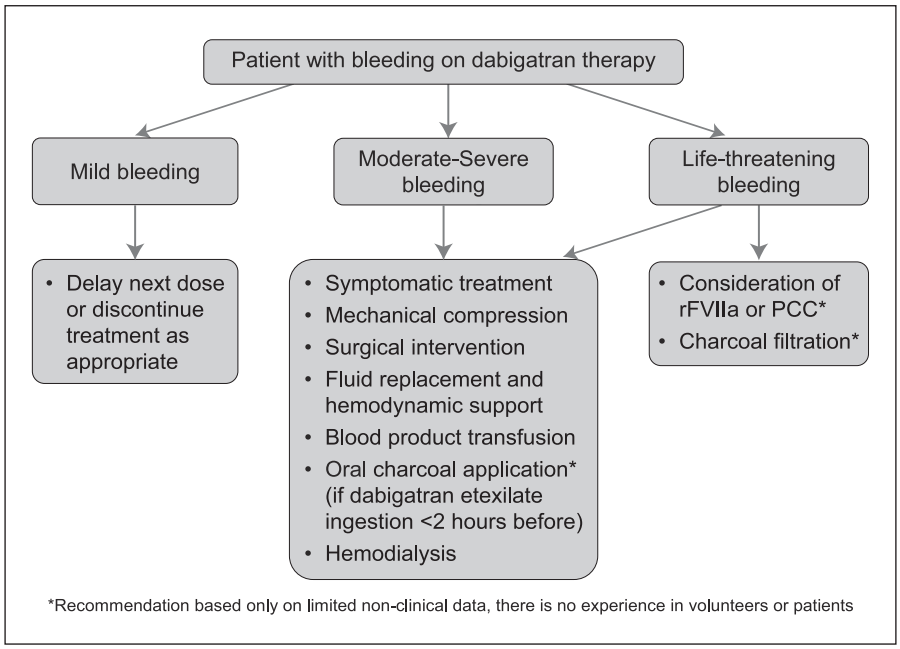

Figure 7: Management of dabigatran in cases of bleeding. PCC = prothrombin complex concentrates (non-activated or activated). rFVIIa = recombinant activated factor VII.

ency situations a risk-benefit evaluation regarding use of this treatment is required.

In a rat tail model of template bleeding (42), addition of APCC (Feiba VH®), at a dose of 50 or 100 U/kg significantly reduced prolongation of BT effects associated with high-dose dabigatran (1 μmol/kg bolus + 0.5 μmol/kg/h infusion for 25 min) (42). APCC at 100 U/kg reduced BT prolongation by dabigatran from 11.6-fold (ratio to control) to 1.4-fold. The aPTT was not shortened in the presence of APCC, consistent with reported data for melagatran (44, 49). Similar findings to those reported with Feiba VH® have recently been shown with non-activated PCC Beriplex® P/N (CSL Behring, Marburg, Germany); using an *ex vivo* rabbit model, bleeding with high dose dabigatran was reduced following the administration of Beriplex® (data on file). Further *in vitro* studies using human plasma show complete reversal of the dabigatran-inhibited endogenous thrombin potential (ETP) with APCC (Feiba VH®) (data on file).

Haemodialysis and haemofiltration

Dabigatran is dialysable due to its relatively low (~35%) plasma protein binding (12). In cases of overdose or severe bleeding, where more rapid reversal of the anticoagulant effects of dabigatran is required, haemodialysis could be effective in accelerating plasma clearance of dabigatran, especially in patients with renal impairment. This is supported by data from an open-label study, in which a single 50 mg dose of dabigatran etexilate was administered to six patients with end-stage renal failure on maintenance haemodialysis (11). Mean inlet- and outlet line dialysis concentrations were 12.6 and 4.4 ng/ml, respectively, at 2 h after dosing and 8.9 and 3.4 ng/ml at 4 h after dosing. Based on the mean concentration differences at the inlet- and outlet lines, the mean fraction of the drug removed by dialysis was 62% at 2 h and 68% at 4 h. Similarly, another study reported efficient elimination of melagatran by haemodialysis in patients with uraemia (glomerular filtration rate <8 ml/min), with seven-fold higher clearance of melagatran during haemodialysis than between dialysis sessions (50). High-volume haemofiltration has also been reported to be effective in reducing hirudin plasma levels (51).

Other options

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of dabigatran. Similarly, there is neither expected benefit nor experience with the use of other systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid and aminocaproic acid) in individuals receiving dabigatran etexilate. This is supported by evidence from preclinical studies which showed that none of these agents efficiently reversed prolonged bleeding induced at very high doses of melagatran (52). Plasma products (e.g. fresh frozen plasma) are often administered in emergency situations to achieve haemostasis in patients who are anticoagulated. However, while they may be as part of usual treatment for bleeding there is no clinical experience or evidence that use of plasma products will reverse the anticoagulant effect of dabigatran.

Conclusions

Dabigatran etexilate is a new oral anticoagulant which has been clinically developed for the prevention and treatment of a range of thromboembolic disorders using fixed-dose regimens without the need for routine coagulation monitoring. In situations where an assessment of the anticoagulant activity of dabigatran or treatment compliance is required various coagulation assays are available. In general, higher dabigatran plasma concentrations result in prolonged clotting times, although some tests are more sensitive compared with others.

Both the TT and ECT tests are highly sensitive tests for measuring the anticoagulant effects of dabigatran, each showing a linear relationship for dabigatran concentrations up to 400 ng/ml. The TT test, however, is probably too sensitive for routine monitoring (especially if 1.5 NIH units of human thrombin are used). A diluted thrombin time assay (Hemoclot® Thrombin Inhibitor assay), using dabigatran standards is another precise, sensitive and robust TT method suitable for the quantitative assessment of dabigatran concentrations in human citrated plasma; however, this test is still under development and not yet commercially available. In addition, further studies in different patient groups are required before this assay can be recommended for monitoring the anticoagulant effects of dabigatran.

Despite the limitations discussed in this paper, the aPTT may be also useful for qualitative assessment, especially in smaller centres where alternative methods are not available. There are limited data on the use of ACT. In emergency situations, the aPTT and TT are the most effective qualitative methods widely available for determining the presence or absence of anticoagulant effect in patients

Key Points

- The TT, Hemoclot® Thrombin Inhibitor test (with dabigatran standards) and ECT tests are sensitive tests for quantitating the anticoagulant effects of dabigatran.
- In emergency situations, the aPTT and TT are the most accessible qualitative methods for monitoring the anticoagulant effects of dabigatran. The aPTT is less sensitive at supratherapeutic concentrations of dabigatran.
- There are limited clinical data with the ACT.
- PT (INR) is less sensitive and cannot be recommended.
- In the case of potential dabigatran overdose, pre-clinical studies suggest that future management options may include the use of activated charcoal, charcoal filtration or haemodialysis. In cases of life-threatening bleeding, administration of rFVIIa or PCC may also be considered.

receiving dabigatran. Prothrombin time (INR) is less sensitive than other assays and cannot be recommended.

In routine clinical practice, very few patients will require the use of an antidote to reverse the anticoagulant effect (53). However, most patients will require supportive treatment to control bleeding. The shorter half-life of dabigatran (12 to 14 h) compared with warfarin (36 to 42 h) may counterbalance the lack of an antidote. It should be noted that the time to reversal of anticoagulation with VKA is not only be affected by their half-life after cessation of treatment, but also by the interval before the production of properly carboxylated coagulation factors that have not been affected by VKA.

In cases of potential overdose with dabigatran, the use of activated charcoal if administered early after ingestion (within 1–2 h) or dialysis may be considered. Elimination of dabigatran with haemodialysis was shown to effectively reduce circulating plasma levels in patients with end-stage renal disease. Where there is life-threatening bleeding and conventional measures have failed or are unavailable, preclinical studies suggest that specific clotting factors including rFVIIa or PCCs or charcoal filtration may have potential for the rapid reversal of anticoagulant effect.

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