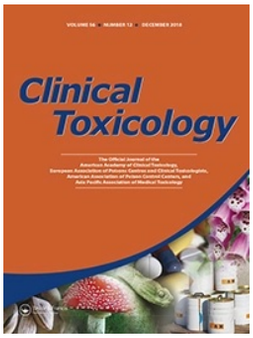

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CLINICAL RESEARCH

Incomplete responses to the recommended dose of idarucizumab: a systematic review and pharmacokinetic analysis

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ABSTRACT

Introduction: Dabigatran, a direct thrombin inhibitor, is 80% renally eliminated and demonstrates multi-compartmental pharmacokinetics. Idarucizumab is a monoclonal antibody that reverses dabigatran-induced anticoagulation and displays single compartment pharmacokinetics, with a smaller volume of distribution and shorter elimination half-life than dabigatran. These differences in pharmacokinetics mean that redistribution of dabigatran from peripheral compartments can occur after idarucizumab has been eliminated, resulting in rebound in the dabigatran plasma concentration and treatment failure. Clinical experience notes failure of a single idarucizumab 5 g dose to fully reverse coagulopathy in certain patients.

Aims: To identify factors predisposing to an incomplete response to the standard idarucizumab 5 g dose.

Methods: A systematic literature search in PubMed using terms "dabigatran" and "idarucizumab" covering 2015 to October 2019 identified 387 entries. Titles and abstracts were screened initially, followed by full text review and data extraction from 97 eligible articles. Data extracted included clinical information, dabigatran concentrations, coagulation results, idarucizumab dosage and patient outcomes. Pharmacokinetic simulations were conducted using a two-compartment model to predict the likelihood that acute or chronic kidney disease will contribute to an incomplete reversal of dabigatran-induced anticoagulation.

Results: Of 240 published cases receiving idarucizumab, 33 reported dabigatran concentration rebound, within a median time of 22 h. From 231 cases reporting idarucizumab dose, 10 received repeated administration due to a rebound in dabigatran concentrations. Baseline dabigatran concentrations >285 ng/mL were more likely to experience a rebound post-idarucizumab to >30 ng/mL (detectable). For baseline dabigatran >488 ng/mL, the concentration rebounded to >75 ng/mL (therapeutic).

The impact of kidney dysfunction on the effect of the recommended dose of idarucizumab: Idarucizumab is expected to neutralise a maximum plasma dabigatran concentration of 980 ng/mL, but most likely a lesser amount. Pharmacokinetic modelling suggests, for patients taking dabigatran 150 mg twice daily, an incomplete response to 5 g idarucizumab is predicted after approximately 72 h dosing when GFR less than 30 mL/min (25% of normal), and after 36 h with severely impaired renal function (GFR 6 mL/min; GFR 5% of normal).

Acute dabigatran self-poisoning: Idarucizumab has neutralised dabigatran following deliberate self-poisoning with dabigatran in a limited number of cases, even in the absence of bleeding. There are insufficient data regarding the use of idarucizumab as part of standard supportive care in this context.

Clinical use of idarucizumab in complex circumstances: The dilute thrombin time can be used to determine the dabigatran concentration, but other more standard coagulation assays are less precise. A normal aPTT largely excludes dabigatran. We suggest performing coagulation assays and dabigatran concentrations every 6 h for a minimum of 36 h after idarucizumab administration to detect a rebound in dabigatran. This is particularly necessary in patients with glomerular filtration rate <30 mL/min or those with a plasma dabigatran concentration exceeding approximately 500 ng/mL. If a rebound in dabigatran is noted, then repeat administration of idarucizumab 5 g can be considered for reversal of recurrent coagulopathy if clinically indicated.

Conclusion: The use of idarucizumab for reversal of dabigatran is complex and requires consideration of clinical circumstances and laboratory investigations. Monitoring post-idarucizumab may be required in acute or chronic kidney disease to detect a rebound in dabigatran concentration and the need for additional doses of idarucizumab.

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Introduction

Dabigatran is a non-vitamin K dependent oral anticoagulant that directly inhibits thrombin. Dabigatran-induced coagulopathy was historically difficult to manage, requiring treatment with renal replacement therapies and coagulation factors [1]. In 2015, the humanised murine monoclonal antibody fragment idarucizumab was approved [2,3] for the rapid reversal of anticoagulant effects of dabigatran for emergency surgery or urgent procedures, or in cases of life threatening or uncontrolled bleeding [4]. The recommended dosage is 5 g (2 × 2.5 g/50 mL vials) given as two consecutive intravenous injections, but additional 5 g doses may be given if there is persistent or recurrent anticoagulation [5]. Idarucizumab binds dabigatran and its glucuronide metabolites with a 350-fold greater affinity than thrombin itself, thereby reversing anticoagulation [6]. Following inactivation of dabigatran and reversal of anticoagulation, the resulting idarucizumab-dabigatran complex is renally eliminated [2].

Since the accelerated approval of idarucizumab in 2015, there have been several case reports of incomplete reversal of dabigatran in patients with life-threatening bleeding following use of the approved idarucizumab dose [3,7–10]. During the phase 3 RE-VERSE AD study, 1.8% of patients received more than a single 5 g dose of idarucizumab [5]. Deaths from the complications of dabigatran-induced coagulopathy have been reported despite the use of idarucizumab [10–13]. Furthermore, an expansion in the clinical use of idarucizumab has been observed, for example in the treatment of acute dabigatran overdose in the absence of active bleeding [14,15], or prior to thrombolysis [16–18].

Dabigatran overdose is the key reason for an incomplete response to idarucizumab. Overdose may be subacute or chronic (for example, in patients with acute or chronic impaired kidney function in the absence of dose adjustment) [12], or in the context of acute self-poisoning.

Finally, the high cost of idarucizumab necessitates consideration of its optimal use.

These observations prompt ongoing reflection on the use of idarucizumab. In particular, it is necessary to anticipate circumstances when the recommended dose of idarucizumab will not fully reverse dabigatran-induced coagulopathy because this may prompt further treatments, including additional doses of idarucizumab.

Here, we briefly review the pharmacokinetics of both dabigatran and idarucizumab and consider the impact of comorbidities including kidney and liver disease. Factors that increase the risk of an incomplete response to the approved dose of idarucizumab will be illustrated through pharmacokinetic modelling and consideration of published reports identified in a systematic literature search. We propose methods for anticipating an incomplete response to idarucizumab within the clinical context.

Methods

To understand the current real-world experience of idarucizumab in reversing dabigatran, we performed a systematic literature search in PubMed using the terms “dabigatran” and “idarucizumab” covering the period 2015 to October 2019. Titles and abstracts were reviewed initially, followed by full text review and data extraction of eligible articles. Articles were considered to be eligible for data extraction if there was use of idarucizumab and individual patient parameters (such as dabigatran concentrations or coagulation parameters) were reported. Articles reporting only aggregate data (such as large cohort studies and phase 1 randomised trials) were excluded from data extraction but were reflected on in the discussion.

From 387 articles identified initially, 97 articles describing 240 individual cases were considered eligible and analysed. A flow diagram of the search strategy is presented according to the Preferred Reporting in Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Figure 1).

For reference, the dabigatran trough concentrations reported in the RE-LY study for patients treated with 150 mg twice daily were median 93 ng/mL (10th to 90th percentile 39.8 to 215 ng/mL) [19]. A therapeutic dabigatran plasma concentration of 75–240 ng/mL has been proposed [20]. However, lower concentrations appear to induce significant coagulopathy. For example, in the phase 3 RE-VERSE AD study, unbound dabigatran concentrations greater than 20 ng/mL (equivalent to approximately 29 ng/mL total dabigatran concentration) were associated with recurrent or continued bleeding which prompted repeat doses of idarucizumab [5].

Pharmacokinetics of dabigatran and idarucizumab

Approximately 20% of dabigatran is conjugated by glucuronosyltransferases to pharmacologically active metabolites (dabigatran-glucuronide) [21]. Idarucizumab binds to and inactivates both the dabigatran parent compound and the glucuronide metabolites in a highly specific manner with no reported off target effects [6,22].

Dabigatran and idarucizumab have markedly differing pharmacokinetics. The volume of distribution of dabigatran (50–70 L) [23] is significantly higher than that of idarucizumab (8.9 L) [24,25]. With normal kidney function, the elimination half-life of idarucizumab is biphasic, initially 45 min with a terminal elimination half-life of 10.3 h, which is slightly shorter than 13 h for dabigatran [26–28]. The half-life for dabigatran is prolonged to a greater extent than idarucizumab with increasing degrees of chronic kidney disease (CKD) (see Table 1).

The implications of these differences in pharmacokinetics are that a significant proportion of dabigatran is located in physiological compartments inaccessible to idarucizumab. When the idarucizumab binding capacity is exceeded, or idarucizumab has been completely eliminated due to its shorter half-life, the dabigatran redistributing from extravascular compartments to the intravascular compartment (central circulation) is not inactivated and a rebound in the dabigatran plasma concentration occurs. Further, given idarucizumab has a high affinity for dabigatran and is highly specific for dabigatran and its active glucuronide metabolite and the resulting complex is stable [22,26,32], dissociation of the

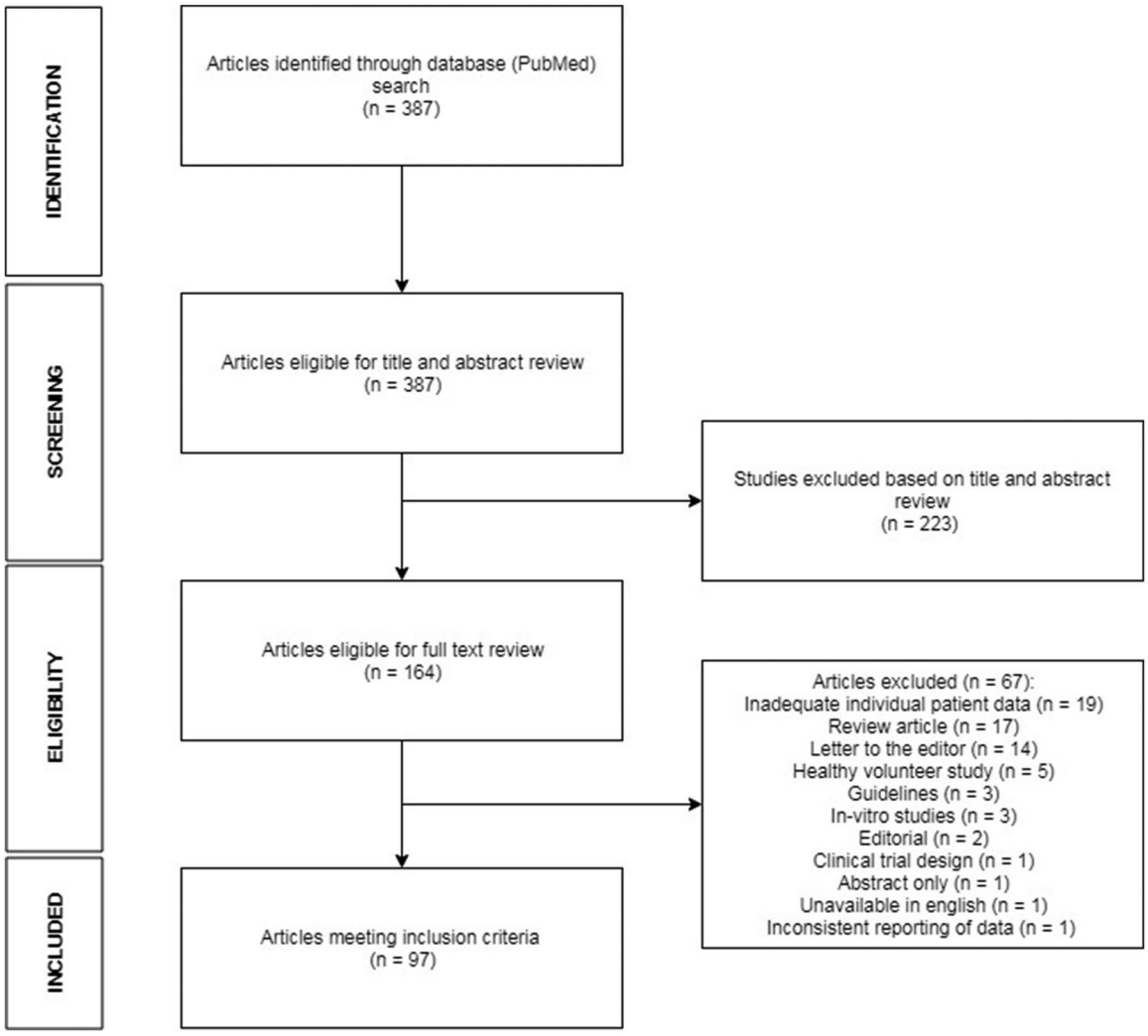

Figure 1. Flowchart of literature search and article identification.

Table 1. Impact of chronic kidney disease on the pharmacokinetics of dabigatran and idarucizumab.

Kidney impairment stage (CrCL, mL/min)	Minimum relative increase in AUC		Elimination half-life (relative increase) (h)		Clearance (mL/min)	
	Idarucizumab [4]	Dabigatran [28]	Idarucizumab [29]	Dabigatran [28]	Idarucizumab [30]	Dabigatran [31]
Normal (>80)	1.0	1.0	10.3 (1.0)	13 (1.0)	47.0	62.9
Mild (51–80)	1.4	1.5	9.5 (0.9)	15 (1.2)	32.8	42.0
Moderate (30–50)	1.9	3.2	10.1 (1.0)	18 (1.4)	25.7	25.6
Severe (10–29)	2.46	6.0	–	27 (2.1)	–	10.3

CrCL: creatinine clearance; AUC: area under the concentration-time curve.

complex would not be expected to contribute to observed rebound. The clinical significance of the limitations of the recommended dose of idarucizumab due to these pharmacokinetic phenomenon is supported by numerous reports in the literature [5,27,33–37].

Rebound of dabigatran is noted in healthy volunteers who were given lower doses of idarucizumab (e.g., 1 g) after only 4 days' dabigatran dosing [37]. A rebound in dabigatran concentrations is also reported after dialysis [1] due to multi-compartmental pharmacokinetics principles [38].

Rationale for the recommended dose of idarucizumab

A phase 1 study in Caucasian subjects confirmed that 2 g of idarucizumab completely neutralised dabigatran at steady state when dosed at 220 mg twice daily for 3–4 days (mean peak steady state concentration of 155 ng/mL) [39]. A phase 1 study in Japanese subjects taking the same dosage as the former study demonstrated that 4 g idarucizumab was required to completely neutralise dabigatran (median peak steady state concentration of 286 ng/mL) [37].

The approved dose of idarucizumab 5 g was selected as it was calculated to neutralise the dabigatran body burden that corresponds to the 99th percentile of plasma dabigatran concentrations associated with therapeutic dabigatran dosing (i.e., 150 mg twice daily) at steady state in patients with mild to moderate renal impairment (creatinine clearance greater than 30 mL/min) during the RE-LY trial (peak plasma concentration less than 500 ng/mL) [19,24,40,41].

A study in volunteers up to 80 years old or with glomerular filtration rate (GFR) down to 30 mL/min taking 150 or 220 mg (depending on the group) dabigatran twice daily for four days demonstrated adequate reversal with idarucizumab 5 g [29].

For reference, in vitro studies have reported a half maximal inhibitory concentration (IC50) of dabigatran for thrombin as 0.56 μmol/L [42]. This is equivalent to 264 ng/mL of dabigatran. In comparison, idarucizumab has an IC50 for dabigatran of 11 nmol/L in human whole blood and an IC50 of 3.1–11 nmol/L in plasma [30].

The anticipated impact of the recommended dose of idarucizumab in kidney dysfunction

Volunteer and observational studies provide valuable insights on the impact of 5 g idarucizumab on dabigatran plasma concentrations. However, they are limited to therapeutic doses in patients without clinically significant comorbidities such as advanced kidney disease. It is useful, therefore, to consider under which circumstances the recommended dose of idarucizumab would be insufficient.

An incomplete resolution of coagulopathy due to idarucizumab occurs when the amount of dabigatran (body burden) exceeds the binding capacity of idarucizumab which is proportional to the idarucizumab dose. Idarucizumab binds an equimolar concentration of dabigatran [22,37], so 5 g idarucizumab is expected to bind 49 mg of dabigatran. Given that dabigatran's steady state volume of distribution is 50 – 70 L [25], this dose is estimated to reflect a plasma concentration between 700 ng/mL and 980 ng/mL at steady state (Box 1). However, these calculations are likely to over-estimate the efficacy of idarucizumab as they assume single compartment pharmacokinetics for both drugs. Instead, dabigatran is characterised by two-compartment kinetics [43] and idarucizumab is largely limited to the central compartment with minimal effect on the second (peripheral) compartment.

Box 1. Calculations for estimating the theoretical effect of idarucizumab on dabigatran plasma concentrations.

Parameter	Idarucizumab	Dabigatran
Molecular weight (Daltons, Da) [25]	47,800	472
Apparent volume of distribution (litres, L) [25]	8.9	50 – 70
Bioavailability (%) [107]	N/A	6.5
Dose administered (grams, g) [4]	5	N/A

Using simple mass-mole calculations, where n = moles, m = mass and M = molar mass, $n = \frac{m}{M} \rightarrow 5/47{,}800 = 1.05 \times 10^{-4}$ moles of idarucizumab in every 5 g dose, $m = n \times M \rightarrow 1.05 \times 10^{-4} \times 472 = 0.049$ g of dabigatran. Therefore, given equimolar binding [22], 5 g idarucizumab is expected to bind 49 mg of dabigatran. Based on the volume of distribution of dabigatran, this correlates with Concentration $= \frac{\text{mass}}{\text{volume}} \rightarrow 49/70$ to $49/50 \rightarrow 0.7$ to 0.98 mg/L $\rightarrow$ 700 to 980 ng/mL

mg: milligrams; ng: nanograms; mL: milliliter.

We modelled the impact of different dabigatran exposures and kidney disease on the effect of a single dose of 5 g idarucizumab using Berkeley Madonna software version 8.3.18 [44]. The pharmacokinetic parameters for dabigatran were based on the biopharmaceutics review of idarucizumab, published by the Food and Drug Administration (FDA) [43], and dabigatran was dosed as 150 mg every 12 h. Idarucizumab was modelled as neutralising a plasma dabigatran concentration of 980 ng/mL, the upper limit of its maximum effect (Box 1). The following conditions were considered:

(1) normal renal function (assumed to be GFR 120 mL/min);
(2) 50% renal function (GFR 60 mL/min);
(3) 25% renal function (GFR 30 mL/min); and
(4) 5% renal function (GFR 6 mL/min).

Both the non-renal clearance and oral bioavailability were assumed to be constant in all simulations. It is acknowledged that dabigatran would be uncommonly prescribed to patients with GFR less than 30 mL/min in the chronic setting, but a GFR this low is certainly observed in acute kidney injury, which is a common scenario when considering the use of idarucizumab. We considered the rebound to be significant when the plasma dabigatran concentration exceeded 30 ng/mL (detectable), or 75 ng/mL which is the proposed lower limit of therapeutic dabigatran concentrations.

The simulated dabigatran concentration-time profiles are shown in Figure 2. It is observed that steady state conditions are achieved within 3 days of dosing (6 doses) in patients with normal (GFR 120 mL/min) renal function. However, a significant increase in the time taken to reach steady state conditions is demonstrated, particularly when GFR is less than 6 mL/min (5% of normal renal function) with failure to achieve steady state even after 7 days of dosing (14 doses).

The response to 5 g idarucizumab after seven days' dabigatran therapy is shown in Figure 2. It is evident that when GFR is less than 30 mL/min (25% of normal renal function) patients are at risk of an incomplete response of idarucizumab. The rebound in dabigatran concentrations post-idarucizumab (Figure 2, iii) reflects idarucizumab completely neutralising dabigatran in the central compartment only, with subsequent dabigatran redistributing from the peripheral compartment. As noted in Figure 2, iv, when GFR is less than 6 mL/min, idarucizumab fails to neutralise dabigatran in the central compartment, with a subsequent increase in dabigatran concentrations due to redistribution.

Figure 3 illustrates the impact of idarucizumab on the dabigatran concentration at differing time points in patients with differing degrees of kidney dysfunction. These reflect either dabigatran therapy in a patient with chronic kidney disease (CKD), or a patient with acute kidney injury (AKI) who continues dabigatran therapy prior to diagnosis of kidney injury and subsequent cessation of dabigatran. For patients taking dabigatran 150 mg twice daily, an incomplete response to 5 g idarucizumab is predicted after approximately 72 h dosing when GFR is less than 30 mL/min (25% of normal). In those with severely impaired kidney function (GFR 5% of normal), an incomplete response is observed after 36 h. In contrast, the standard dose of idarucizumab appears to be acceptable in those with GFR greater than

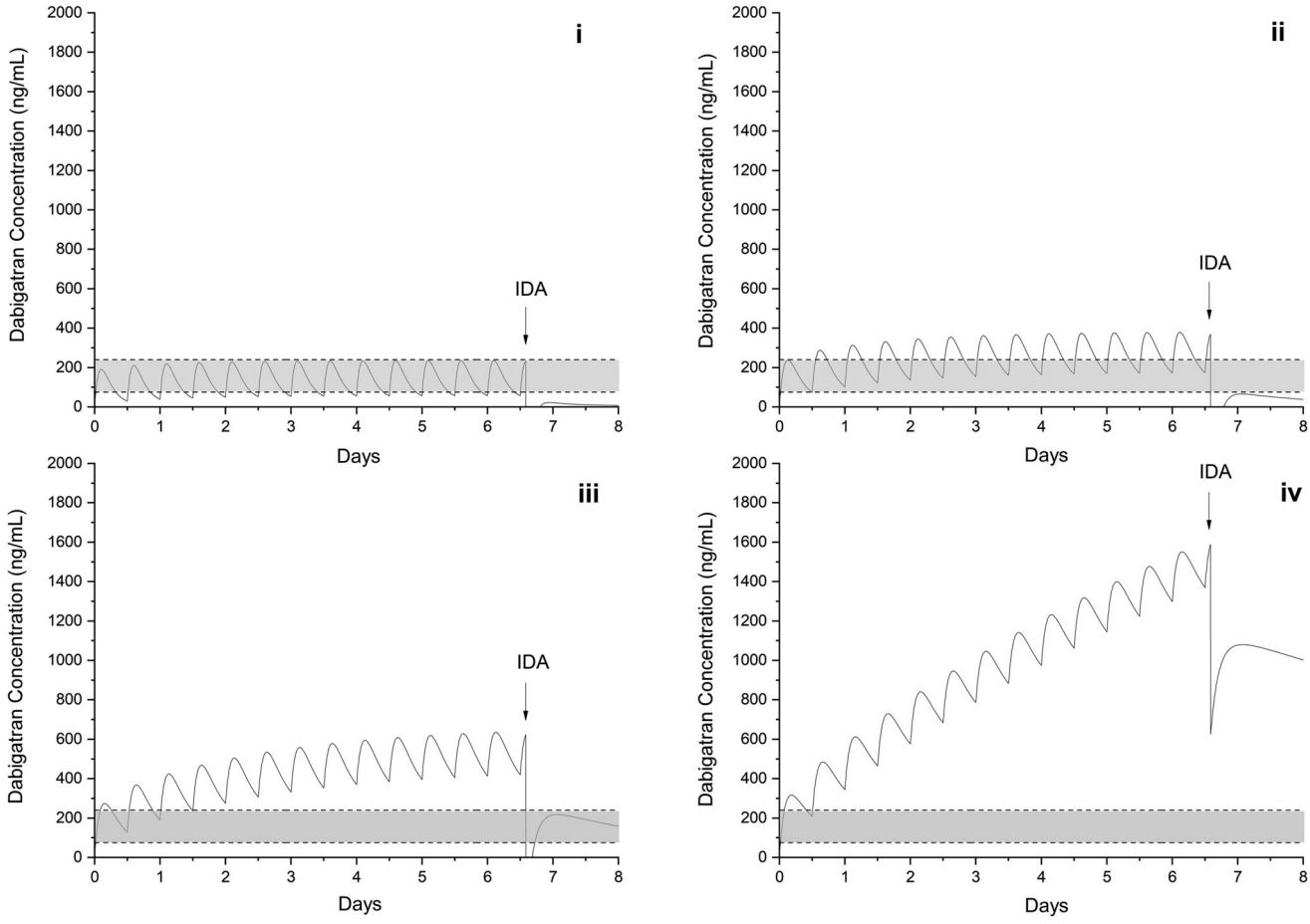

Figure 2. The effect of kidney function and 5 g idarucizumab on plasma dabigatran concentrations (dabigatran 150 mg twice daily). Shaded areas represent the proposed therapeutic range (75–240 ng/mL). i. Normal renal function (GFR 120 mL/min). ii. 50% renal function (GFR 60 mL/min). iii. 25% renal function (GFR 30 mL/min). iv. 5% renal function (GFR 6 mL/min).

30 mL/min, which is also consistent with observations in volunteer studies.

These simulations confirm that the presence of moderate to severe kidney dysfunction for as little as three days predicts an incomplete response to the recommended dose of idarucizumab 5 g.

The volume of distribution of dabigatran (50–70 L; measured by intravenous administration) [45] is substantially larger than idarucizumab (8.9 L). However, it is uncertain whether the volume of distribution changes with kidney dysfunction because available data are limited to studies with oral dosing which cannot account for changes in bioavailability. For example, in a small volunteer study, the mean apparent volume of distribution with oral dosing was 3120 L with healthy volunteers, decreasing to 1220 L in patients with more severe kidney disease and then increasing to 5040 L in those with end-stage renal disease [31]. Therefore, changes in the volume of distribution of dabigatran with kidney dysfunction is based on minimal data so its impact on idarucizumab dosing is poorly defined. Inter-individual variability in bioavailability across disease states such as kidney disease is also described for other drugs [46].

Note that these predictions are based on mean pharmacokinetic variables and other assumptions already described, therefore the observed impact may be somewhat different due to inter-individual variability. Additionally, these simulations do not account for the increased exposure to idarucizumab that may be seen with impaired renal function (Table 1) which may cause a lesser degree of rebound. Further, these simulations assume that dabigatran therapy was commenced on day zero, so in cases of AKI in the context of chronic dosing, the initial dabigatran concentration will be higher and thus the effect of idarucizumab will be less than shown in Figures 2 and 3.

The effect of idarucizumab observed in clinical use

Idarucizumab 5 g adequately reversed dabigatran-induced anticoagulation on the basis of the dilute thrombin time (dTT) or activated partial thromboplastin time (aPTT) in the peri-procedural setting in patients with therapeutic dosing but without significant comorbidities [11,47–51]. Despite idarucizumab treatment, deaths occurred in 8.7% ($n = 21$) [3,8,10–13,17,18,52–59] of individual cases, and 19% ($n = 42$) in the case series with aggregated data [60–68].

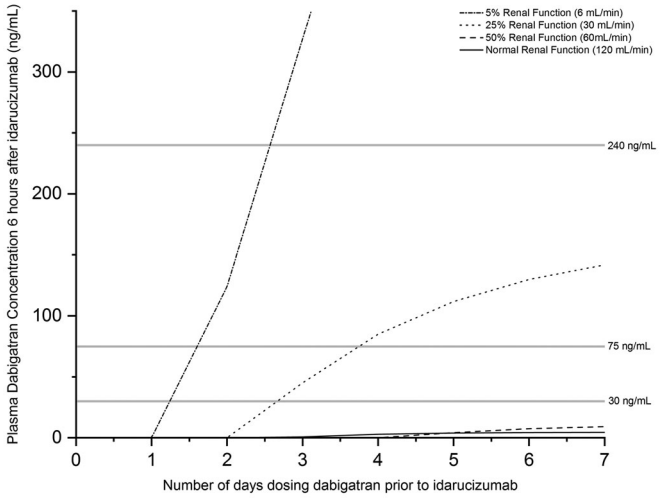

Figure 3. Simulated plasma dabigatran concentrations 6 h following idarucizumab administration stratified according to kidney function and number of days dosing dabigatran.

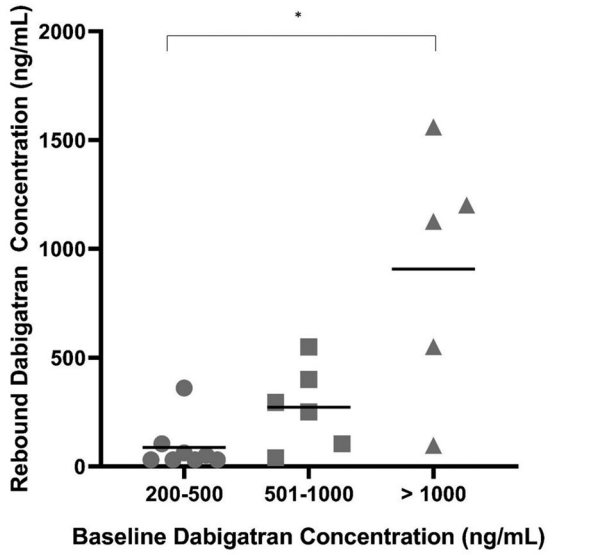

Figure 4. Rebound concentrations of dabigatran following idarucizumab administration stratified by baseline (pre-idarucizumab) concentration of dabigatran ($n = 19$). Unless otherwise specified, undetected concentrations or concentrations reported as 'less than threshold' were assumed as 30 ng/mL. Black lines represent median. Cases of acute dabigatran self-poisoning have been excluded. *($p = 0.0025$) [Kruskal-Wallis Test].

The administration of additional doses of idarucizumab for a rebound in dabigatran concentrations

A number of publications have reported repeat dosing of idarucizumab for incomplete inactivation of dabigatran [7,11,57,69–75]. For example, a case with an initial dabigatran concentration of 2044 ng/mL required a cumulative dose of idarucizumab up to 15 g to neutralize the effects of dabigatran [75]. Here, a significant rebound in dabigatran concentrations occurred after each dose of idarucizumab, to a maximum of 551 ng/mL with associated bleeding. Four subsequent doses of idarucizumab 2.5 g were administered when dabigatran concentrations exceeded 100 ng/mL.

This was similar to other reports by Simon et al. [3], Marino et al. [7], McBride et al. [70] and Sheikh-Taha [71] where repeat doses of idarucizumab were administered following a rebound in dabigatran concentrations. Repeat doses were administered to nine patients in the RE-VERSE AD study due to rebound dabigatran concentrations associated with bleeding [5,49]. Furthermore, based on data available from 231 cases of idarucizumab use in the literature, (where idarucizumab dose was reported) repeat doses of idarucizumab were required in 10 of these (4.3%). Of these cases, 5 were administered a total of 10 g, 1 received 12.5 g and a further 4 were administered 15 g. In the case series and cohort studies that reported aggregate data (excluding RE-VERSE AD), of 589 patients administered idarucizumab, 10 (1.7%) required doses exceeding 5 g [60–68,76,77].

Initial dabigatran concentrations associated with a rebound post-idarucizumab

Although it is estimated that 5 g idarucizumab can bind dabigatran in steady state plasma concentrations up to 980 ng/mL (Box 1), case reports describe a net decrease in dabigatran plasma concentrations of more than 1000 ng/mL [15], up to 1600 ng/mL (non-sustained) [3] and more than 2000 ng/mL (non-sustained) [36,73,75] in both adults and children (aged 15 years). Other reports have noted that a single dose of idarucizumab was ineffective at fully inactivating dabigatran due to high initial concentrations exceeding 1500 ng/mL, but further doses were not administered [11,36].

A review of 16 patients proposed that patients with a baseline dabigatran concentration less than 200 ng/mL did not experience a significant rebound in dabigatran post-idarucizumab [57]. We identified 19 patients on chronic therapy with sufficient appropriate data to assess for a rebound, where a dabigatran concentration-response relationship to idarucizumab was observed, Figure 4 [3,35,36,54,57,72,73,75,78–81]. A rebound in dabigatran plasma concentrations is detected (peak rebound greater than 30 ng/mL) when the pre-idarucizumab dabigatran concentration is greater than 228 ng/mL (likelihood ratio 3.7) (Figures 4 and 5).

The risk of a significant rebound (peak rebound greater than 75 ng/mL, therapeutic) is high when the pre-idarucizumab concentration exceeds 500 ng/mL (likelihood ratio 5.8 for dabigatran plasma concentration greater than 487.5 ng/mL) with chronic therapy (Figures 4 and 5). Patients with dabigatran plasma concentrations greater than 1000 ng/mL appear to be at particularly high risk of rebound post-idarucizumab 5 g (Figure 4). Indeed, the degree of dabigatran redistribution can be extensive [27]. For example, an initial plasma dabigatran concentration of 1630 ng/mL decreased to less than 30 ng/mL following idarucizumab, but eight hours later rebounded to 1560 ng/mL (96% of the pre-idarucizumab concentration) [3].

Onset of the rebound in dabigatran concentration

The time that the rebound is detected, and the extent to which it occurs, is anticipated to depend on the ratio between the dabigatran body burden and dose of idarucizumab. Rebound is commonly observed within 6 to 24 h (but up to 72 h) of 4–5 g idarucizumab administration with chronic dosing of dabigatran, but it can occur earlier with

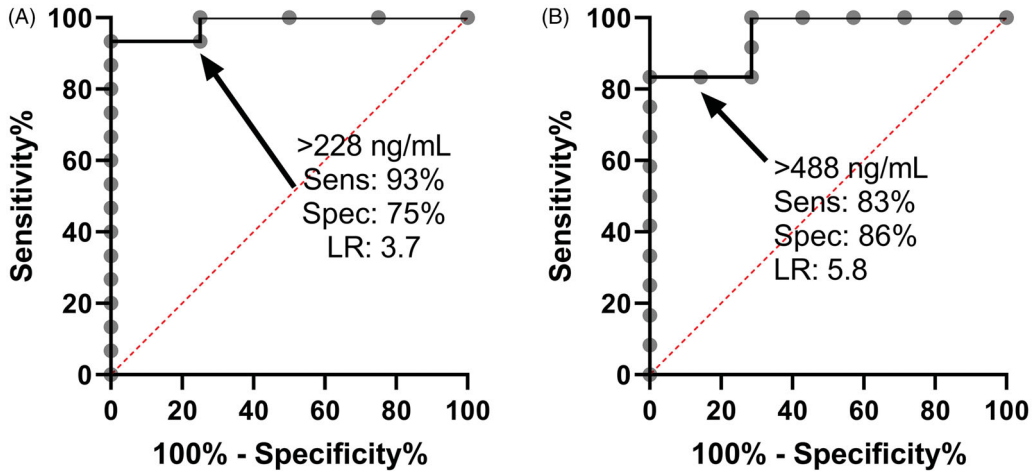

Figure 5. Receiver-operating characteristic curves showing the influence of the pre-idarucizumab dabigatran concentration on the extent of the rebound concentration. A, for rebound (>30 ng/mL) post-idarucizumab (AUC 0.98); B, for rebound >75 ng/mL post-idarucizumab (AUC 0.95). Sens: sensitivity; spec: specificity; LR: likelihood ratio; AUC: area under the receiveroperating characteristic (ROC) curve.

lower idarucizumab doses and/or higher dabigatran exposures [3,5,8,27,33–35,37,57,75,81,82].

A rebound in dabigatran concentrations post-idarucizumab has been observed in both AKI and CKD, with an onset of 6-8 h post-idarucizumab in more severe AKI, or over 12 h in those with lesser degrees of AKI [33,34,41]. Furthermore, previous case reports have demonstrated peak rebound dabigatran concentrations after 12 – 30 h in patients with impaired kidney function [3,35,75]. This finding is supported by data extracted from 33 cases (see Figure 1) in the literature where dabigatran rebound was documented (either in the form of abnormal coagulation tests or elevated dabigatran concentrations above the lower limit of detection of the assay). The vast majority of cases where significant rebound was observed were associated with impaired kidney function. The median time of dabigatran rebound was 22 h (IQR 12–42) after idarucizumab administration. Here, depending on the clinical situation and laboratory testing, repeated idarucizumab doses or other treatments such as haemodialysis may be required.

Comorbidities

There is a paucity of data confirming efficacy of single dose idarucizumab in populations with acute or chronic conditions of varying severity. Case reports and series provide useful insights into the potential benefits and limitations of idarucizumab in certain circumstances. However, multiple treatments, including extracorporeal treatment and clotting factor replacement were administered concomitantly in a number of publications, making it difficult to ascertain the relative clinical impact of each treatment, including idarucizumab [7,12,74,83,84].

Kidney disease

Kidney disease imparts unequal changes in the pharmacokinetics of dabigatran and idarucizumab, as summarised in Table 1. It is notable that area under curve (AUC) and elimination half-life do not change proportionately. The increase in dabigatran AUC in CKD is not offset by the increase in idarucizumab AUC, and dabigatran's elimination half-life is more prolonged. In volunteer studies there are complex and inconsistent changes in volume of distribution and the maximum dabigatran concentration with more severe kidney disease, but both probably increase [31]. The bioavailability of dabigatran is less than 10% due to P-glycoprotein [20,85], but P-glycoprotein activity may decrease in patients with CKD, increasing the bioavailability [86]. The same principles may also apply in acute kidney injury (AKI). Therefore, patients with CKD or AKI are at increased risk of dabigatran accumulation [46] and over-anticoagulation which predisposes to idarucizumab failure (Figures 2 and 3). Of note, dabigatran is reported to potentially induce AKI, possibly due to glomerular haemorrhage [87].

Clinical use of idarucizumab in patients with impaired kidney function confirms the higher risk of incomplete reversal from a standard dose of idarucizumab [55,60].

Liver disease

A study comparing twelve participants with Child Pugh B cirrhosis against matched controls demonstrated no change to dabigatran peak plasma concentration (C_{max}), area under the curve (AUC), or glucuronidation. It also demonstrated that the relationships between plasma dabigatran concentrations and aPTT and TT were preserved, while the sensitivity of INR was increased, likely reflecting the underlying liver impairment [88]. There is a lack of data on the effects of acute liver injury on dabigatran and idarucizumab pharmacokinetics.

Liver impairment, both acute and chronic, can lead to a hypocoagulable state [89] which will increase the risk of bleeding associated with dabigatran and make interpretation of standard laboratory assays more challenging. The primary assay used in dabigatran monitoring, the dilute thrombin time (dTT), is not influenced by hepatic impairment because control plasma is used to determine dabigatran concentrations [90]. Consequently, in patients presenting with bleeding who are suspected to have ingested dabigatran, dTT can be accurately used to guide the role of idarucizumab.

Importantly, patients with persistent bleeding and elevated aPTT, prothrombin time (PT) or international normalised ratio (INR), but normal dTT will not benefit from idarucizumab.

Other considerations

Other factors may also impact dabigatran concentrations, although data confirming their clinical significance are limited. For example, drugs which inhibit P-glycoprotein such as amiodarone, dronedrone, voriconazole, ketoconazole, posaconazole and itraconazole may increase the dabigatran concentration [91]. Conversely, enzyme inducers such as carbamazepine, phenobarbital, phenytoin and rifampicin may lower the dabigatran concentration, as can obesity [91,92]. Coadministration of antiplatelet drugs may also have an additive impact on bleeding which will not be estimated in the coagulation studies discussed here [93].

Clinical use of idarucizumab in complex circumstances

Repeated or higher doses of idarucizumab have been shown to be safe and are required in certain circumstances in order to achieve complete reversal of dabigatran [7,11,57,69–75]. However, repeat doses of idarucizumab have not previously been considered clinically necessary in many cases where there was a rebound in dabigatran post-idarucizumab [11,36]. Therefore, the decision for repeat idarucizumab dosing should be made on a case-by-case basis.

It is anticipated that in cases of overdose due to dosing errors or medical comorbidities (kidney or liver disease) that the initial dabigatran concentration will guide the potential need for repeat doses of idarucizumab. Guidelines for predicting patients who are likely to experience a rebound in dabigatran concentrations post-idarucizumab are lacking, and likely to be very complex given the many factors contributing to this. When plasma dabigatran concentrations exceed 200 ng/mL [57], the frequency and cumulative dose of idarucizumab required to reverse all coagulopathy is poorly defined. However, it is more likely to be required when greater than 500 ng/mL and particularly when exceeding 1000 ng/mL (Figure 4).

Routine coagulation studies

Idarucizumab reversal of dabigatran-induced anticoagulation can be confirmed by coagulation assays and dabigatran concentrations [26]. Since, dabigatran concentrations are not widely available it is useful to consider the utility of more routine coagulation studies. In general, such laboratory studies are mostly used to confirm that dabigatran is present, for example in the assessment of a patient with active bleeding or following idarucizumab administration. Potentially, they may also indicate when a standard dose of idarucizumab may be inadequate.

The more readily available tests include the activated partial thromboplastin (aPTT), international normalised ratio (INR) or prothrombin time (PT), the thrombin time (TT) and dilute thrombin time (dTT) [94,95], and each of these can be prolonged by dabigatran. A number of these coagulation studies, particularly TT and dTT are sensitive to the effect of dabigatran, even at relatively low drug concentrations.

The dTT is directly proportional to the concentration of dabigatran and has been utilised for a commercially available dabigatran plasma assay [96]. The sensitivity of the dTT is reduced for dabigatran plasma concentrations less than 50 ng/mL [26] so it is an unreliable test to exclude a potentially clinically significant dabigatran concentration. Further, its use is limited by accessibility.

The relationship between dabigatran concentration and aPTT is curvilinear, with flattening of the curve at dabigatran concentrations greater than 200 ng/mL [90,97,98]. As such, aPTT provides a semi-quantitative prediction of the dabigatran concentration at lower concentrations with less precision at higher concentrations. Chronic treatment with dabigatran has a pre-dose aPTT that is 1.5–2 times the population reference range [50]. An aPTT exceeding 90–100 s corresponds to a dabigatran concentration greater than 500 ng/mL [90,99]. A normal aPTT excludes the presence of a clinically significant concentration of dabigatran [29,97].

The international normalised ratio (INR) has a linear relationship with plasma dabigatran concentrations [97,98]. The INR is not elevated (greater than 1.2) until plasma dabigatran concentrations exceed 62 ng/mL [97] and an INR of 2.0 correlates with a plasma concentration of approximately 400 ng/mL, which is supratherapeutic [98]. Therefore, INR cannot be used to exclude the presence of dabigatran [97,100] but an elevated INR may indicate a supratherapeutic concentration.

Of 240 cases reporting use of idarucizumab, rebound in dabigatran was assessed using a variety of parameters including plasma dabigatran concentrations, aPTT, INR and TT measurements. The reporting of rebound using coagulation assays were highly heterogeneous with some cases reporting only one coagulation test result. Of 240 cases, 24 reported rebound aPTT measurements with a median of 84.73 s (IQR 44.30–104.70). Fifteen reported rebound INR with a median of 1.97 (IQR 1.24–3.00) and 20 reported rebound TT with a median of 85 s (IQR 58.26–135.75). These results are approximately equal to rebound dabigatran concentrations of 510 ng/mL, 375 ng/mL and >600 ng/mL respectively [97].

Unfortunately, although these relationships are reported in different institutions across the world, they may not always be applicable. Multiple studies have demonstrated that with therapeutic dabigatran concentrations there is considerable variability and imprecision in both aPTT and PT/INR assays depending on the reagent used [92,101,102]. Therefore, clinicians should check whether data are available for the assay performed at their institution.

Comorbidities

In patients with kidney and liver disease, the use of idarucizumab should be based on clinical features such as bleeding or need for emergent surgery or procedure, haematology testing, serum biochemistry (including liver function and kidney function) and plasma dabigatran concentrations. In

particular, higher doses of idarucizumab may be required to completely inactivate dabigatran which accumulates when there is impaired kidney function [5].

Active bleeding does not stop immediately following reversal of dabigatran by idarucizumab [5,9,26]. Other interventions in addition to controlling the bleeding source may also be indicated, including blood products such as factor eight inhibitor bypassing activity (FEIBA) and red cell transfusion and renal replacement therapies [1,33,103,104].

Assessing the need for additional doses of idarucizumab

It is reasonable to measure haematological parameters (see previous section) and dabigatran concentrations (if available) every 6 h for a minimum of 36 h after idarucizumab administration to determine if additional idarucizumab is required [3,34,35,75]. This approach will allow for early detection of the onset, and peak rebound dabigatran concentrations. In reports where repeat doses of idarucizumab were administered, the median time to onset of rebound in dabigatran anticoagulation was 22 h (IQR 16.5–33.0; range 4–72 h) [7,57,69–73]. While most of these cases used dabigatran concentrations to determine rebound, some used less sensitive markers of dabigatran induced coagulopathy such as aPTT or INR, as dabigatran concentrations were not readily available [7,69].

Acute dabigatran self-poisoning

Early administration of idarucizumab in cases of acute dabigatran self-poisoning may neutralise dabigatran prior to its distribution to peripheral compartments, thereby being relatively more effective despite a high plasma dabigatran concentration. This theory is supported on the basis of two cases of deliberate self-poisoning. An adult ingested 18,750 mg dabigatran etexilate and the standard idarucizumab 5 g dose reduced the plasma unbound dabigatran concentration from 643 ng/mL (approximately equal to 918 ng/mL total dabigatran concentration) to zero with normalisation of coagulation assays, both of which were sustained for 24 h [14]. A 15-year-old ingested 4500 to 7500 mg of dabigatran etexilate with a resulting dabigatran plasma concentration exceeding 1000 ng/mL. Following idarucizumab 5 g, dabigatran was completely neutralised with a minor clinically insignificant rebound 15 h later, in the absence of bleeding [15].

More data are required to better define the risks and benefits of treating acute dabigatran poisoning with idarucizumab. Cost considerations including the duration of observation and blood testing in an acute setting between conservative management and idarucizumab remain to be clarified [105]. However, early administration is likely to be more effective. It is also reasonable to perform haematology testing (dTT, aPTT) and plasma dabigatran concentrations (if available) every 6 h for a minimum of 36 h post-idarucizumab to recognise and consider treatment of any rebound.

Restarting dabigatran

Previous studies have demonstrated that if clinically indicated, dabigatran can be recommenced 24 h after reversal using idarucizumab in healthy volunteers [106]. While restarting dabigatran 24 h after reversal may be appropriate in healthy volunteers, the presence of dabigatran rebound will prevent re-initiation of dabigatran therapy in those with more severe kidney disease. Additionally, factors such as bleeding risk, illness states, medical co-morbidities and ongoing absorption will substantially alter the timing of resolution of toxicity and recommencement of dabigatran in clinical practice.

Future research

Currently, determining total body burden of dabigatran remains a challenge; therefore, defining the dose increments above 5 g idarucizumab remains difficult. Future studies utilising pharmacokinetic modelling may provide further insight into individualised dosing in complex circumstances as well as alternate methods of idarucizumab administration. It is possible that in some cases the rebound in dabigatran is related to the relatively short half-life of idarucizumab, such that it was eliminated prior to binding with redistributed dabigatran, thereby wasting some of the idarucizumab dose. Intravenous infusions of idarucizumab may be a more efficient use of this drug and minimise the extent of the rebound in dabigatran concentrations compared with that observed with bolus injection, as has been noted in some scenarios [38,46]. In other circumstances, it may be advantageous to also initiate haemodialysis to enhance the elimination of dabigatran [70].

Conclusion

The use of idarucizumab for reversal of dabigatran in patients is complex, requiring consideration of clinical circumstance, haematological and biochemical investigations and plasma dabigatran concentrations. Given the imposing cost of idarucizumab, cost benefit considerations will ultimately influence its widespread use as an antidote.

Author Contributions

Akshay Athavale – design and implementation of study, pharmacokinetic modelling, data extraction, statistical analyses, writing of manuscript. Nazila Jamshidi – planning and oversight of study, writing and revision of manuscript. Darren M Roberts – oversight and design and implementation of study, writing and revision of manuscript. Takes overall responsibility for the paper

Disclosure statement

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