Intern Emerg Med (2009) 4:137–145
DOI 10.1007/s11739-008-0201-8

EM - REVIEW

Emergency reversal of antithrombotic treatment

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Received: 8 September 2008 / Accepted: 3 October 2008 / Published online: 12 November 2008

Abstract The most important adverse effect of antithrombotic treatment is the occurrence of bleeding. In case of serious or even life-threatening bleeding in a patient who uses anticoagulant agents or when a patient on anticoagulants needs to undergo an urgent invasive procedure, anticoagulant treatment can be reversed by various specific strategies. Heparin and heparin derivatives can be counteracted by protamine sulphate, whereas the anticoagulant effect of vitamin K antagonists may be neutralized by administration of vitamin K or prothrombin complex concentrates. The anti-hemostatic effect of aspirin and other anti-platelet strategies can be corrected by the administration of platelet concentrate or desmopressin, if needed. Recently, a new generation of anticoagulants with a greater specificity towards activated coagulation factors has been introduced and most of these agents are presently being evaluated in clinical studies. The new generation anticoagulants include specific inhibitors of factor IIa, factor Xa (including pentasaccharides) and agents that interfere with tissue factor activity. A limitation of this new class of anticoagulants may be the lack of an appropriate strategy to reverse the effect if a bleeding event occurs, although in some cases the administration of recombinant factor VIIa may be an option.

Keywords Anticoagulants · Hemorrhage · Heparin · Pentasaccharides · Vitamin K antagonists · Aspirin · Clopidogrel · IIb–IIIa inhibitors

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Introduction

Anticoagulant agents are often used for prevention and treatment of a wide range of cardiovascular diseases. Most frequently used anticoagulants are heparin or its derivatives, vitamin K antagonists (such as warfarin or coumadin) and antiplatelet agents, including aspirin and thienopyridine derivatives, such as clopidogrel. A myriad of clinical studies demonstrate that these agents (alone or in combination) can prevent or treat acute or chronic thromboembolic complications, such as in patients with atrial fibrillation or prosthetic heart valves, after myocardial infarction or ischemic stroke, and in patients with venous thrombosis or pulmonary embolism [1]. The most important complication of treatment with anticoagulants is hemorrhage, which may be serious, may cause long-term debilitating disease, or may even be life-threatening [2]. In well-controlled patients in clinical trials treatment with vitamin K antagonists increases the risk of major bleeding by 0.5%/year and the risk of intracranial hemorrhage by about 0.2%/year [3]. In a very large series of 34,146 patients with acute ischemic coronary syndromes, anticoagulant-associated bleeding is associated with a fivefold increased risk of death during the first 30 days and a 1.5-fold higher mortality between 30 days and 6 months [4]. Major bleeding is an independent predictor of mortality across all subgroups that are analyzed. In some clinical situations the incidence of serious bleeding complications may annihilate or even overwhelm the efficacy of antithrombotic agents, as has been shown in the secondary prevention of patients with ischemic stroke by vitamin K antagonists [5]. Nevertheless, in many situations, clinical studies show a favorable balance between efficacy and safety in favor of anticoagulant treatment. However, if severe bleeding occurs, or if a patient needs to undergo an

urgent invasive procedure, such as emergency surgery, it may be required to reverse the anticoagulant effect of the various agents. Depending on the clinical situation, i.e., the severity of the bleeding or the urgency and estimated risk of the invasive procedure, this reversal may take place in a few h, but in some cases immediate reversal is necessary (Table 1). Generally, each (immediate) reversal of anticoagulant treatment needs also to take into consideration the indication for the antithrombotic agents. For example, the interruption of combined aspirin and clopidogrel treatment in a patient in whom an intracoronary stent has been recently inserted will markedly increase the risk of acute stent thrombosis with consequent downstream cardiac ischemia or infarction. Likewise, in a patient with a prosthetic mitral valve and atrial fibrillation, interruption of vitamin K antagonists may increase the risk of valve thrombosis and cerebral or systemic embolism. Each of these specific clinical situations requires a careful and balanced assessment of the benefits and risks of reversing anticoagulants (and potential strategies to keep the period of reversal as short as possible). In this article, we will describe the various strategies to reverse the anticoagulant effect of currently most widely used antithrombotic agents and some new anticoagulants.

Heparin and low molecular weight (LMW) heparin

Herparin and heparin derivatives act by binding to antithrombin, and thereby about 1,000-fold potentiating the anticoagulant effect of this endogenous inhibitor towards thrombin and factor Xa (and some other coagulation factors). Heparin has a relatively short half-life of about 60–90 min, and therefore the anticoagulant effect of therapeutic doses of heparin will be mostly eliminated at 3–4 h after termination of continuous intravenous administration [6]. The anticoagulant effect of high dose subcutaneous heparin, however, will take a longer time to cease. If a more immediate neutralization of heparin is required, intravenous protamine sulphate is the antidote of choice. Protamine, derived from fish sperm, binds to heparin to form a stable biologically inactive complex. Each milligram of protamine will neutralize approximately 100 units of heparin. Hence, the protamine dose in a patient on a stable therapeutic heparin dose of 1,000–1,250 U/h should be about 25–30 mg (sufficient to block the amount of heparin given in the last 2–3 h). The maximum dose of protamine is 50 mg. Since the half-life of protamine is only about 10 min, the reversal of a therapeutic dose of subcutaneous heparin requires a repeated infusion of protamine sulphate (e.g., repeated after 1 h). The

Table 1 Commonly used anticoagulants and their antidotes

	Time until restoration of hemostasis after cessation of therapeutic dose	Antidote	Remark
Heparin	3–4 h	Protamine sulphate 25–30 mg; immediate reversal	One milligram of protamin per 100 anti-Xa units given in the last 2–3 h
LMW heparin	12–24 h	(Partially) protamine sulphate 25–50 mg; immediate reversal	One milligram of protamine per 100 anti-Xa units given in the last 8 h
Pentasaccharides	Fondaparinux 24–30 h Idraparinux 5–15 days	Recombinant factor VIIa 90 ug/kg (?); immediate thrombin generation	Based on laboratory end-points, no systematic experience in bleeding patients
Vitamin K antagonists	Acenocoumarol 18–24 h Warfarin 60–80 h Phenprocoumon 8–10 days	Vitamin K i.v: reversal in 12–16 h Vitamin K orally: reversal in 24 h PCC': immediate reversal	Dose of vitamin K or PCCs depend of INR and bodyweight
Oral thrombin and factor Xa inhibitors	Dependent of compound, usually within 12 h	Recombinant factor Xa for Xa inhibitors, unsure for IIa inhibitors	Based on laboratory end-points, no systematic experience in bleeding patients
Aspirin	5–10 days (time to produce unaffected platelets)	DDAVP (0.3–0.4 ug/kg) and/or platelet concentrate; reversal in 15–30 min	Cessation not always required, also dependent on clinical situation and indication
Clopidogrel	1–2 days	Platelet concentrate, possibly in combination with DDAVP (0.3–0.4 ug/kg); reversal in 15–30 min	Cessation not always desirable, also dependent on clinical situation and indication
IIb/IIIa inhibitors	Dependent of preparation, usually within 24 h	Platelet concentrate, possibly in combination with DDAVP (0.3–0.4 ug/kg); reversal in 15–30 min	

LMW heparin low molecular weight heparin, *PCC* prothrombin complex concentrate, *DDAVP* de-amino D-arginin vasopressin or desmopressin

effect of protamine can be monitored by measuring the activated partial thromboplastin time (aPTT), which should normalize after the protamine administration.

The reversal of LMW heparin is more complex, as protamine sulphate will only neutralize the anti-factor IIa activity, and has no or only partial effect on the smaller heparin fragments causing the anti-factor Xa activity of the compound [7, 8]. The net effect of protamine reversal of LMW heparin is not completely clear. There are no clinical studies that have systematically studied this, and small case series and experimental animal studies show contradictory results [8–10]. As the aPTT is not useful as a monitoring assay when using LMW heparin, it can also not be used for the monitoring of the neutralizing effect of protamine. Given the relatively long half-life of LMW heparin, the lack of an adequate strategy to reverse its anticoagulant action may sometimes cause a problem in clinical situations. A practical approach is to give 1 mg of protamine per 100 anti-factor Xa units of LMW heparin given in the last 8 h (where 1 mg of enoxaparin equals 100 anti-factor Xa units). If bleeding continues, a second dose of 0.5 mg per 100 anti-factor Xa units can be given.

The most important adverse effect of protamine is an allergic response, including hemodynamic and respiratory problems [11]. Most adverse reactions can be prevented or minimized by slowing the rate of administration of the drug or by pretreatment with steroids and antihistamines. Risk factors for an adverse reaction are sensitivity to fish (as may occur in traditional fishermen who are often exposed to fish proteins when cutting themselves), a history of vasectomy (which may demolish the blood–testis barrier with consequent formation of anti-semen antibodies) and a history of receiving protamine sulphate containing insulin. Initial reports that the use of protamine sulphate could lead to an increased risk of rebound thrombosis, in particular ischemic stroke [12, 13] are not confirmed in a recent randomized controlled study [14].

There are some other strategies to reverse (mostly unfractionated) heparin, such as platelet factor-4, heparanase, or extracorporeal heparin-removal devices, but none of these approaches have been properly evaluated, and they are not currently approved for clinical use [15–17].

Pentasaccharides

Pentasaccharides are recently developed synthetic compounds that effectively bind and potentiate antithrombin to block factor Xa. Since they lack the additional glycosaminoglycan saccharide residues to bind to thrombin, it has an effect on factor Xa exclusively. The prototype pentasaccharide (and the only one approved for clinical use so far) is fondaparinux. Another pentasaccharide that is currently under study is idraparinux. The main difference between these two agents is in the elimination of half-life, which is 15–20 h for fondaparinux and 5½ days for idraparinux. This means that idraparinux can be administered once weekly, which renders the subcutaneous route of administration less cumbersome. Pentasaccharides are effective in the prophylaxis and treatment of venous thromboembolism, and are currently being evaluated in other types of thrombosis [18]. The (very) long half-life of pentasaccharides necessitates the availability of a suitable antidote if major bleeding complicates the treatment, which may especially occur in patients who are treated with therapeutic doses of this type of anticoagulation. So far, there is no antidote for pentasaccharides that has been studied in controlled clinical studies [19]. The only agent that has been systematically evaluated to reverse the anticoagulant effect of pentasaccharides is recombinant factor VIIa (rVIIa). Two randomized placebo-controlled studies in healthy volunteers have tested the hypothesis that rVIIa may be useful as a suitable antidote for pentasaccharide anticoagulation [20, 21]. In the first study 16 subjects were treated with therapeutic doses of the pentasaccharide fondaparinux and after 2 h (at the time of maximal anticoagulation) challenged with rVIIa or placebo. Injection of rVIIa (90 μg/kg) after fondaparinux normalizes the prolonged aPTT and prothrombin time (PT) and reverses the decrease in prothrombin activation fragments $1 + 2$ ($F(1 + 2)$), as observed with fondaparinux alone. Thrombin-generation time and endogenous thrombin potential, which were inhibited by fondaparinux, normalize in up to 6 h after rVIIa injection. In the second study, 12 subjects received a single subcutaneous dose of 7.5 mg idraparinux, (which is threefold higher than the currently recommended dose). The inhibition of thrombin generation by idraparinux, as reflected by an increased thrombin generation time (TGT) and decreased level of prothrombin fragment $1 + 2$ (F_{1+2}), is partially reversed by injection of rVIIa 3 h after idraparinux administration. The administration of rVIIa 1 week after treatment with idraparinux (when much lower, though still therapeutic, doses of the pentasaccharide are present) results in a nearly complete reversal of anticoagulation, reflected by normalization of thrombin generation time and other markers of thrombin generation. As mentioned earlier, there are no controlled trials in patients who present with pentasaccharide-induced bleeding, but there is some anecdotal experience suggesting that rVIIa may indeed be able to stop bleeding in patients anticoagulated with fondaparinux.

Vitamin K antagonists

Vitamin K antagonists interfere with the γ-carboxylation of glutamate residues on vitamin K-dependent proteins, which

therefore are not capable of a calcium-dependent conformational change by which they can bind to phospholipid surfaces, resulting in a strongly reduced coagulant activity [22]. There are several vitamin K antagonists available, of which warfarin is most widely used, but also the coumadin derivatives acenocoumarol and phenprocoumon are frequently prescribed. The most important difference between these three agents is their half-life, which is 9 h for acenocoumarol, 36–42 h for warfarin, and 90 h for phenprocoumon, respectively. This variation in half-lives may have important consequences for the optimal strategy to reverse each of these agents. The time to reversal of anticoagulation with vitamin K antagonists will not only be affected by their half-life after cessation of treatment, but also by the time it will take to produce properly carboxylated coagulation factors that have not been affected by vitamin K antagonists.

Vitamin K antagonists are potent anticoagulants and it is recommended to not perform major surgical procedures when the patient is fully anticoagulated. In these situations the anticoagulant treatment needs to be interrupted or its intensity should be considerably reduced. Perioperative prophylaxis of venous thromboembolism can be achieved by administration of subcutaneous (LMW) heparin.

The most straightforward intervention to counteract the effect of vitamin K antagonists is the administration of vitamin K [23, 24]. Whereas there is quite some debate on the use of vitamin K in patients with a too high intensity of anticoagulation (i.e., a too high INR) but no signs of bleeding, in patients with clinically significant bleeding administration of vitamin K is crucial to reverse the anticoagulant effect of warfarin or coumadin derivatives. Vitamin K can be given orally and intravenously, whereas despite a reasonably quick and good systemic bioavailability of oral vitamin K, the parenteral route has the advantage of a more rapid onset of the treatment [25–31]. After the administration of intravenous vitamin K, within 2 h the INR will start to drop and will be completely normalized within 12–16 h [31], whereas after oral administration it will take up to 24 h to normalize the INR [23, 32]. Intramuscular injections of vitamin K should be avoided in patients who are anticoagulated (since they may cause muscle bleeding) and subcutaneous administration of vitamin K results in a less predictable bioavailability [25, 27]. When the INR is below seven, a dose range of 2.5–5 mg vitamin K has been advocated to completely counteract the anticoagulant effect, whereas with higher INRs a dose of 5–10 mg is required to correct the INR. Higher doses of vitamin K are equally effective but may lead to warfarin or coumadin resistance for more than a week, which may hamper long-term management of these patients [33]. Of note, when reversal of anticoagulation has to be sustained for a longer period, repeated administration of vitamin K may be required, especially in patients who use vitamin K antagonists with a long half-life, such as phenprocoumon. A potential concern with the use of parenteral vitamin K is the occurrence of anaphylactic reactions, although the incidence of this complication is very low, in particular with the more modern micelle preparations [34–36]. To avoid this, a low infusion rate (e.g., 1 mg/3 min) has been advocated [23].

In case of very serious or even life-threatening bleeding, immediate correction of the INR is mandatory, and can be achieved by the administration of vitamin K-dependent coagulation factors. Theoretically, these factors are present in fresh frozen plasma; however, the amount of plasma that is required to correct the INR is very large, carries the risk of fluid overload, and will probably take hours to administer [37, 38]. Therefore, prothrombin complex concentrates (PCCs), containing all vitamin K-dependent coagulation factors, are more useful. In a small study in patients using vitamin K antagonists who needed urgent reversal of anticoagulation because of major bleeding or emergency invasive procedures, PCCs at a fixed dose of 500 U are sufficient to correct INR values <5.0. However, at INR values >5 higher doses are required [39]. Although PCCs can indeed be given using fixed dose schemes [40], it has been shown that individualized dosing regimens based on INR at presentation and body weight are more effective [41]. In a prospective cohort study of patients who presented with major bleeding associated with the use of vitamin K antagonists patients were treated with PCCs at a relatively high dose of 25–50 U/kg (exact dose per patient was "based on the INR and severity of bleeding"), which was effective in reducing the INR below 2 in 56 out of 58 patients [42, 43]. Another prospective study in patients using vitamin K antagonist and presenting with bleeding or the need for an urgent invasive procedure necessitating normalization of the INR also finds that doses of PCCs in a similar dose range are effective in reducing the INR below 1.3 in 93% of patients and results in at least satisfactory and sustained hemostasis in 98% [44]. In this study, the dose of PCCs was tailored to the INR at presentation (INR 2–4 25 U/kg, INR 4–6 35 U/kg, and INR >6 50 U/kg, respectively).

PCCs can be given over a short time frame, have an immediate effect, and the efficacy of the reversal of anticoagulation can be monitored by measuring the INR. PCCs are shown to be safe in a series of 14 retrospective and prospective cohort studies encompassing 460 patients [45]. Thrombo-embolic complications occurred in seven patients although in most cases this could have been explained by the underlying clinical situation and co-morbidity as well. In recent years the safety of PCCs, in particular regarding the transmission of blood-borne infectious diseases, has markedly improved owing to several techniques, such as

pasteurization, nanofiltration, and addition of solvent detergent. The often stated risk of disseminated intravascular coagulation (DIC) due to traces of activated coagulation factors in PCCs comes from older literature, and modern PCCs seem not to be associated with eliciting or aggravating DIC [46].

Another option for immediate correction of the INR in patients using vitamin K antagonists is the administration of rVIIa, although this treatment is not officially approved for this indication. In healthy volunteers who were treated with the vitamin K antagonist acenocoumarol, the prolongation of the international normalized ratio (INR) above 2.0 was normalized with the administration of rVIIa at doses between 5 and 320 μg/kg [47]. The duration of the INR correction is dependent on the dose of rVIIa, whereby doses of rVIIa larger than 120 μg/kg result in an INR normalization that lasts longer than 24 h. Correction of the INR after administration of rVIIa may be a "cosmetic" effect since the prothrombin time is very sensitive towards traces of VIIa in plasma; however, a small clinical study finds that rVIIa at a dose of 16 μg/kg results in satisfactory hemostasis in 14 out of 16 patients who presented with major bleeding while using vitamin K antagonists [48]. Another study demonstrates that reversal of warfarin anticoagulation in a series of 13 patients undergoing invasive procedures results in a normalization of the prothrombin time and prevents bleeding in all subjects [49] and a series of six patients with central nervous system bleeding due to treatment with vitamin K antagonists showed successful reversal of anticoagulation, arrest of bleeding and uncomplicated drainage in all patients after administration of rVIIa [50].

New anticoagulants

In recent years a large number of new antithrombotic agents has been developed and tested in clinical trials, and many of these new agents will become available for clinical practice in the very near future [51]. The need for new anticoagulant agents is quite obvious; first, the current agents are insufficiently effective. For example 10–15% of patients undergoing major orthopedic surgery develop venous thromboembolism, despite prophylaxis with low molecular weight (LMW) heparin [52]. Furthermore, the available anticoagulants are relatively unsafe, mostly due to the occurrence of bleeding as discussed earlier. Last, current anticoagulant agents are often cumbersome in regard to their clinical use, requiring repeated laboratory control and frequent dose adjustments. Increasing knowledge on the function of the hemostatic system in vivo has resulted in a new generation of anticoagulant agents. Despite the fact that most of these agents indeed have a somewhat more advantageous benefit-risk profile and are much more easy to use with no need for monitoring or dose adjustments, bleeding remains the most important adverse effect of any type of anticoagulant treatment [53, 54].

An important group of new anticoagulants is the class of direct thrombin inhibitors. Thrombin is the central enzyme in the coagulation process, not only mediating the conversion of fibrinogen to fibrin, but also being the most important physiological activator of platelets and various other coagulation factors. Inhibition of thrombin can be achieved by administration of heparin, but in view of the limited capability of the heparin–antithrombin complex to inhibit surface-bound thrombin, new antithrombin-independent anticoagulants have been developed [55]. Prototype of these thrombin inhibitors is hirudin, originally derived from the saliva from leeches (*Hirudo medicinalis*), and nowadays produced by recombinant technology. Melagatran is a synthetic thrombin inhibitor, which has predictable pharmacokinetic properties and can thus be used in a fixed dose [56]. Moreover, the pro-drug ximelagatran is relatively quickly absorbed after oral ingestion and results in a sufficient systemic availability, rendering this agent suitable for long-term use as oral anticoagulant. Clinical trials on prevention and treatment of venous thromboembolism and in patients with atrial fibrillation showed promising efficacy of (xi)melagatran; however, due to the occurrence of enhanced liver enzymes in 6–7% of patients using melagatran, the compound has been withdrawn by the manufacturer. Nevertheless, there are many similar compounds under evaluation in clinical trials at this moment [57]. None of these compounds has an established antidote available in case of serious bleeding complicating the anticoagulant treatment. In a controlled clinical study in healthy subjects the melagatran-induced effects on aPTT, thrombin generation, and platelet activation are not affected by the administration of rVIIa [58]. Based on these results it seems that rVIIa is not effective in reversing direct thrombin inhibition. Since, however, rVIIa was able to correct the melagatran-induced prolongation of the prothrombin time and increased thrombin precursor protein concentrations, it might be that higher doses of rVIIa will have some effect in this situation, but this needs to be studied in future experiments.

Another class of new anticoagulants is directed at factor Xa. Prototype of these agents are rivaroxaban and apixaban, which have shown promising results in initial experimental and clinical studies [59, 60] There is no evidence of any antidote towards the anticoagulant effect of any of these orally available factor Xa inhibitors so far. Based on the experience with rVIIa in the reversal of the anticoagulant effect of fondaparinux, one can postulate that rVIIa may be an effective antidote for these agents; however, direct proof has not been demonstrated.

In view of the central role of the tissue factor–factor VIIa pathway in the initiation of blood coagulation, novel therapeutic strategies aimed at inhibiting this catalytic complex are currently being evaluated. One of these inhibitors is recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a potent and selective inhibitor of the tissue factor–factor VIIa complex in the presence of factor Xa [61]. This compound shows promising antithrombotic properties in clinical trials of prevention and treatment of venous thromboembolism and percutaneous coronary interventions [62, 63]. Recent reports from in vitro studies indicate that therapeutic doses of recombinant factor VIIa (rVIIa) may be able to induce activation of coagulation resulting in subsequent thrombin generation, possibly independent of tissue factor activity [64, 65]. In a double-blind, randomized, placebo-controlled crossover study, administration of rNAPc2 causes a prolongation of the prothrombin time, which is immediately and completely corrected by the subsequent injection of rVIIa [66]. Administration of rVIIa in the presence of NAPc2 results in a marked generation of thrombin, as reflected by plasma levels of prothrombin fragment F1+2 and thrombin–antithrombin levels, respectively.

Aspirin

Aspirin is effective in the secondary prevention of atherothrombotic disease, in particular coronary artery disease, cerebrovascular thromboembolism and peripheral arterial disease [67]. As a consequence, aspirin is one of the most widely used agents in the Western world. Aspirin increases the risk of bleeding, in particular gastro-intestinal bleeding, and has been associated with a small but consistent increase in intracerebral hemorrhage. In addition, it has been shown that the use of aspirin is associated with increased perioperative blood loss in major procedures, although this does not necessarily translate into clinically relevant endpoints, such as the requirement for transfusion or re-operation [68]. Over the last few years the approach to the patient who uses aspirin and who presents with bleeding or needs to undergo an invasive procedure has changed considerably. In fact, in current clinical practice bleeding can almost always be managed with local hemostatic procedures or conservative strategies without interrupting aspirin. Also most invasive procedures do not require the cessation of aspirin when adequate attention is given to local hemostasis. In contrast, interruption of aspirin has been associated with an increased risk of thromboembolic complications, potentially due to a rebound hypercoagulability [69]. Obviously, in special clinical circumstances, such as intracranial bleeding or the need to undergo a neurosurgical or ophthalmic procedure, the anti-hemostatic effect of aspirin needs to be reversed immediately. The most rigorous measure to achieve that is the administration of platelet concentrate after cessation of aspirin. Another approach is the administration of de-amino D-arginin vasopressin (DDAVP, desmopressin). DDAVP is a vasopressin analogue that despite minor molecular differences has retained its antidiuretic properties, but has much less vaso-active effects [70]. DDAVP induces release of the contents of the endothelial cell associated Weibel Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII) and (also by yet unexplained additional mechanisms) a remarkable augmentation of primary hemostasis as a consequence. DDAVP is effective in patients with mild hemophilia A or von Willebrand's disease and in patients with qualitative platelet defects, such as in uremia or liver cirrhosis. DDAVP seems also capable of correcting the aspirin-induced platelet dysfunction, although large clinical studies employing relevant outcome parameters are missing [71]. The combined effect of platelet concentrate and subsequent administration of DDAVP has also been advocated to correct the aspirin effect on platelets. The standard dose of DDAVP is 0.3–0.4 μg/kg in 100 ml saline over 30 min and its effect is immediate.

Thienopyridine derivatives and other antiplatelet agents

Clopidogrel belongs to the class of thienopyridine derivatives, which act by blocking the ADP receptor on the platelet. Clinical studies have shown that clopidogrel is as good as aspirin in the secondary prevention of atherothrombotic events [72]. However, the combination of aspirin and clopidogrel is superior to aspirin alone in patients who have received intracoronary stents or in other patients with high risk coronary artery disease. The increased efficacy of the combined use of aspirin and clopidogrel is also associated with a higher bleeding risk [73]. The decision whether to interrupt or even reverse antithrombotic treatment with clopidogrel and aspirin in case of serious bleeding or the need to perform an invasive procedure will depend not only on the specific clinical situation but also on the indication for the antithrombotic treatment (see above). Especially in patients with recent implantation of an intracoronary stent (in the last 6–12 weeks), cardiologists will often not or only reluctantly agree with cessation of treatment [74]. In this period re-endothelialization of the stent has not yet occurred and the patient is very vulnerable to acute thrombotic occlusion of the stent. In patients with drug-eluting stents this period

may be even longer. If, however, the decision is made to stop and even reverse the treatment with aspirin and clopidogrel, administration of platelet concentrate is probably the best way to correct the hemostatic defect [75]. In addition, DDAVP was shown to correct the defect in platelet aggregation caused by clopidogrel, so this may be another option [76].

Other antiplatelet agents, which are predominantly used in interventional cardiology, include IIb–IIIa receptor antagonists, such as abciximab or eptifibatide. These agents have a very potent antiplatelet effect and although rare, may carry the risk of thrombocytopenia. If in these situations serious bleeding occurs, administration of platelet concentrate, possibly in combination with DDAVP, will correct the hemostatic defect [77].

Conclusion

Conventional anticoagulant treatment can be reversed by specific interventions when the clinical situation requires immediate correction of hemostasis. For the new generation of anticoagulants, no specific antidotes are available; although some interventions are promising they need further evaluation. Antiplatelet therapy with aspirin can be reversed, but this is often not required. More potent antiplatelet strategies can be counteracted with correcting strategies as well; however, this may in some cases not be desirable in view of the indication for this treatment.

Conflict of interest statement The author declares that he has no conflict of interest related to the publication of this manuscript.

References

1. Hirsh J, Guyatt G, Albers GW, Harrington R, Schunemann HJ (2008) Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 133:110S–112S
2. Mannucci PM, Levi M (2007) Prevention and treatment of major blood loss. N Engl J Med 356:2301–2311
3. Schulman S, Beyth RJ, Kearon C, Levine MN (2008) Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 133:257S–298S
4. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S (2006) Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 114:774–782
5. Algra A (2007) Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet Neurol 6:115–124
6. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI (2008) Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 133:141S–159S
7. Lindblad B, Borgstrom A, Wakefield TW, Whitehouse WM Jr, Stanley JC (1987) Protamine reversal of anticoagulation achieved with a low molecular weight heparin. The effects on eicosanoids, clotting and complement factors. Thromb Res 48:31–40
8. Massonnet-Castel S, Pelissier E, Bara L, Terrier E, Abry B, Guibourt P, Swanson J, Jaulmes B, Carpentier A, Samama M (1986) Partial reversal of low molecular weight heparin (PK 10169) anti-Xa activity by protamine sulfate: in vitro and in vivo study during cardiac surgery with extracorporeal circulation. Haemostasis 16:139–146
9. Van Ryn-McKenna J, Cai L, Ofosu FA, Hirsh J, Buchanan MR (1990) Neutralization of enoxaparine-induced bleeding by protamine sulfate. Thromb Haemost 63:271–274
10. Bang CJ, Berstad A, Talstad I (1991) Incomplete reversal of enoxaparin-induced bleeding by protamine sulfate. Haemostasis 21:155–160
11. Caplan SN, Berkman EM (1976) Letter: protamine sulfate and fish allergy. N Engl J Med 295:172
12. Fearn SJ, Parry AD, Picton AJ, Mortimer AJ, McCollum CN (1997) Should heparin be reversed after carotid endarterectomy? A randomised prospective trial. Eur J Vasc Endovasc Surg 13:394–397
13. Mauney MC, Buchanan SA, Lawrence WA, Bishop A, Sinclair K, Daniel TM, Tribble CG, Kron IL (1995) Stroke rate is markedly reduced after carotid endarterectomy by avoidance of protamine. J Vasc Surg 22:264–269
14. Dellagrammaticas D, Lewis SC, Gough MJ (2008) Is heparin reversal with protamine after carotid endarterectomy dangerous? Eur J Vasc Endovasc Surg 36:41–44
15. D'Ambra M (1996) Restoration of the normal coagulation process: advances in therapies to antagonize heparin. J Cardiovasc Pharmacol 27 (suppl 1):S58–S62
16. Despotis GJ, Summerfield AL, Joist JH, Goodnough LT, Santoro SA, Zimmermann JJ, Lappas DG (1994) In vitro reversal of heparin effect with heparinase: evaluation with whole blood prothrombin time and activated partial thromboplastin time in cardiac surgical patients. Anesth Analg 79:670–674
17. Tao W, Deyo DJ, Brunston RL Jr, Vertrees RA, Zwischenberger JB (1998) Extracorporeal heparin adsorption following cardiopulmonary bypass with a heparin removal device—an alternative to protamine. Crit Care Med 26:1096–1102
18. Buller HR (2002) Treatment of symptomatic venous thromboembolism: improving outcomes. Semin Thromb Hemost 28(suppl 2):41–48
19. Crowther MA, Warkentin TE (2008) Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood 111:4871–4879
20. Bijsterveld NR, Moons AH, Boekholdt SM, van Aken BE, Fennema H, Peters RJ, Meijers JC, Buller HR, Levi M (2002) Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. Circulation 106:2550–2554
21. Bijsterveld NR, Vink R, van Aken BE, Fennema H, Peters RJ, Meijers JC, Buller HR, Levi M (2004) Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. Br J Haematol 124:653–658
22. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G (2008) Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 133:160S–198S
23. Dentali F, Ageno W, Crowther M (2006) Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. J Thromb Haemost 4:1853–1863

24. Baglin T (1998) Management of warfarin (coumarin) overdose. Blood Rev 12:91–98
25. Whitling AM, Bussey HI, Lyons RM (1998) Comparing different routes and doses of phytonadione for reversing excessive anticoagulation. Arch Intern Med 158:2136–2140
26. Watson HG, Baglin T, Laidlaw SL, Makris M, Preston FE (2001) A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. Br J Haematol 115:145–149
27. Crowther MA, Douketis JD, Schnurr T, Steidl L, Mera V, Ultori C, Venco A, Ageno W (2002) Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy. A randomized, controlled trial. Ann Intern Med 137:251–254
28. Weibert RT, Le DT, Kayser SR, Rapaport SI (1997) Correction of excessive anticoagulation with low-dose oral vitamin K1. Ann Intern Med 126:959–962
29. Nee R, Doppenschmidt D, Donovan DJ, Andrews TC (1999) Intravenous versus subcutaneous vitamin K1 in reversing excessive oral anticoagulation. Am J Cardiol 83:286–287
30. Raj G, Kumar R, McKinney WP (1999) Time course of reversal of anticoagulant effect of warfarin by intravenous and subcutaneous phytonadione. Arch Intern Med 159:2721–2724
31. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D (2003) Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 163:2469–2473
32. Dezee KJ, Shimeall WT, Douglas KM, Shumway NM, O'malley PG (2006) Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. Arch Intern Med 166:391–397
33. van Geest-Daalderop JH, Hutten BA, Pequeriaux NC, de Vries-Goldschmeding HJ, Rakers E, Levi M (2007) Invasive procedures in the outpatient setting: managing the short-acting acenocoumarol and the long-acting phenprocoumon. Thromb Haemost 98:747–755
34. Martin JC (1991) Anaphylactoid reactions and vitamin K. Med J Aust 155:851
35. Fiore LD, Scola MA, Cantillon CE, Brophy MT (2001) Anaphylactoid reactions to vitamin K. J Thromb Thrombolysis 11:175–183
36. Dentali F, Ageno W (2004) Management of coumarin-associated coagulopathy in the non-bleeding patient: a systematic review. Haematologica 89:857–862
37. Aguilar MI, Hart RG, Kase CS, Freeman WD, Hoeben BJ, Garcia RC, Ansell JE, Mayer SA, Norrving B, Rosand J, Steiner T, Wijdicks EF, Yamaguchi T, Yasaka M (2007) Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. Mayo Clin Proc 82:82–92
38. Makris M, Greaves M, Phillips WS, Kitchen S, Rosendaal FR, Preston EF (1997) Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. Thromb Haemost 77:477–480
39. Yasaka M, Sakata T, Naritomi H, Minematsu K (2005) Optimal dose of prothrombin complex concentrate for acute reversal of oral anticoagulation. Thromb Res 115:455–459
40. Junagade P, Grace R, Gover P (2007) Fixed dose prothrombin complex concentrate for the reversal of oral anticoagulation therapy. Hematology 12:439–440
41. van AL, Eijkhout HW, Kamphuis JS, Dam M, Schattenkerk ME, Schouten TJ, Ploeger B, Strengers PF (2006) Individualized dosing regimen for prothrombin complex concentrate more effective than standard treatment in the reversal of oral anticoagulant therapy: an open, prospective randomized controlled trial. Thromb Res 118:313–320
42. Lankiewicz MW, Hays J, Friedman KD, Tinkoff G, Blatt PM (2006) Urgent reversal of warfarin with prothrombin complex concentrate. J Thromb Haemost 4:967–970
43. Kessler CM (2006) Urgent reversal of warfarin with prothrombin complex concentrate: where are the evidence-based data? J Thromb Haemost 4:963–966
44. Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H (2008) Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J Thromb Haemost 6:622–631
45. Leissinger CA, Blatt PM, Hoots WK, Ewenstein B (2008) Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am J Hematol 83:137–143
46. Levi M (2007) Disseminated intravascular coagulation. Crit Care Med 35:2191–2195
47. Erhardtsen E, Nony P, Dechavanne M, Ffrench P, Boissel JP, Hedner U (1998) The effect of recombinant factor VIIa (NovoSeven) in healthy volunteers receiving acenocoumarol to an International Normalized Ratio above 2.0. Blood Coagul Fibrinolysis 9:741–748
48. Dager WE, King JH, Regalia RC, Williamson D, Gosselin RC, White RH, Tharratt RS, Albertson TE (2006) Reversal of elevated international normalized ratios and bleeding with low-dose recombinant activated factor VII in patients receiving warfarin. Pharmacotherapy 26:1091–1098
49. Deveras RA, Kessler CM (2002) Reversal of warfarin-induced excessive anticoagulation with recombinant human factor VIIa concentrate. Ann Intern Med 137:884–888
50. Sorensen B, Johansen P, Nielsen GL, Sorensen JC, Ingerslev J (2003) Reversal of the International Normalized Ratio with recombinant activated factor VII in central nervous system bleeding during warfarin thromboprophylaxis: clinical and biochemical aspects. Blood Coagul Fibrinolysis 14:469–477
51. Levi M (2005) New antithrombotics in the treatment of thromboembolic disease. Eur J Intern Med 16:230–237
52. Strebel N, Prins M, Agnelli G, Buller HR (2002) Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? Arch Intern Med 162:1451–1456
53. Bauer KA, Hawkins DW, Peters PC, Petitou M, Herbert JM, van Boeckel CA, Meuleman DG (2002) Fondaparinux, a synthetic pentasaccharide: the first in a new class of antithrombotic agents—the selective factor Xa inhibitors. Cardiovasc Drug Rev 20:37–52
54. Heit JA, Colwell CW, Francis CW, Ginsberg JS, Berkowitz SD, Whipple J, Peters G (2001) Comparison of the oral direct thrombin inhibitor ximelagatran with enoxaparin as prophylaxis against venous thromboembolism after total knee replacement: a phase 2 dose-finding study. Arch Intern Med 161:2215–2221
55. Weitz JI, Buller HR (2002) Direct thrombin inhibitors in acute coronary syndromes: present and future. Circulation 105:1004–1011
56. Wahlander K, Lapidus L, Olsson CG, Thuresson A, Eriksson UG, Larson G, Eriksson H (2002) Pharmacokinetics, pharmacodynamics and clinical effects of the oral direct thrombin inhibitor ximelagatran in acute treatment of patients with pulmonary embolism and deep vein thrombosis. Thromb Res 107:93–99
57. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Buller HR (2007) Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 370:949–956

58. Woltz M, Levi M, Sarich TC, Bostrom SL, Ericksson UG, Erikkson M, Svensson M, Weitz JI, Elg M, Wahlander K (2004) Effect of recombinant factor VIIa on melagatran-induced inhibition of thrombin generation and platelet activation in healthy volunteers Thromb Haemost 91(6):1090–1096
59. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S (2007) Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in patients with acute symptomatic deep-vein thrombosis) study. Circulation 116:180–187
60. Shantsila E, Lip GY (2008) Apixaban, an oral, direct inhibitor of activated Factor Xa. Curr Opin Investig Drugs 9:1020–1033
61. Stassens P, Bergum PW, Gansemans Y, Jespers L, Laroche Y, Huang S, Maki S, Messens J, Lauwereys M, Cappello M, Hotez PJ, Lasters I, Vlasuk GP (1996) Anticoagulant repertoire of the hookworm *Ancylostoma caninum*. Proc Natl Acad Sci USA 93:2149–2154
62. Moons AH, Peters RJ, Bijsterveld NR, Piek JJ, Prins MH, Vlasuk GP, Rote WE, Buller HR (2003) Recombinant nematode anticoagulant protein c2, an inhibitor of the tissue factor/factor VIIa complex, in patients undergoing elective coronary angioplasty. J Am Coll Cardiol 41:2147–2153
63. Lee A, Agnelli G, Buller H, Ginsberg J, Heit J, Rote W, Vlasuk G, Costantini L, Julian J, Comp P, van der MJ, Piovella F, Raskob G, Gent M (2001) Dose-response study of recombinant factor VIIa/tissue factor inhibitor recombinant nematode anticoagulant protein c2 in prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. Circulation 104:74–78
64. Allen GA, Hoffman M, Roberts HR, Monroe DM III (2002) Recombinant activated factor VII: its mechanism of action and role in the control of hemorrhage. Can J Anaesth 49:S7–S14
65. Hedner U, Erhardtsen E (2002) Potential role for rFVIIa in transfusion medicine. Transfusion 42:114–124
66. Friederich PW, Levi M, Bauer KA, Vlasuk GP, Rote WE, Breederveld D, Keller T, Spataro M, Barzegar S, Buller HR (2001) Ability of recombinant factor VIIa to generate thrombin during inhibition of tissue factor in human subjects. Circulation 103:2555–2559
67. Patrono C, Baigent C, Hirsh J, Roth G (2008) Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 133:199S–233S
68. Merritt JC, Bhatt DL (2004) The efficacy and safety of perioperative antiplatelet therapy. J Thromb Thrombolysis 17:21–27
69. Ferrari E, Benhamou M, Cerboni P, Marcel B (2005) Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 45:456–459
70. Richardson DW, Robinson AG (1985) Desmopressin. Ann Intern Med 103:228–239
71. Reiter RA, Mayr F, Blazicek H, Galehr E, Jilma-Stohlawetz P, Domanovits H, Jilma B (2003) Desmopressin antagonizes the in vitro platelet dysfunction induced by GPIIb/IIIa inhibitors and aspirin. Blood 102:4594–4599
72. Anonymous (1996) A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee (see comments). Lancet 348:1329–1339
73. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494–502
74. Grines CL, Bonow RO, Casey DE Jr, Gardner TJ, Lockhart PB, Moliterno DJ, O'Gara P, Whitlow P (2007) Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. Catheter Cardiovasc Interv 69:334–340
75. Vilahur G, Choi BG, Zafar MU, Viles-Gonzalez JF, Vorchheimer DA, Fuster V, Badimon JJ (2007) Normalization of platelet reactivity in clopidogrel-treated subjects. J Thromb Haemost 5:82–90
76. Leithauser B, Zielske D, Seyfert UT, Jung F (2008) Effects of desmopressin on platelet membrane glycoproteins and platelet aggregation in volunteers on clopidogrel. Clin Hemorheol Microcirc 39:293–302
77. Reiter R, Jilma-Stohlawetz P, Horvath M, Jilma B (2005) Additive effects between platelet concentrates and desmopressin in antagonizing the platelet glycoprotein IIb/IIIa inhibitor eptifibatide. Transfusion 45:420–426