Anesthetic implications of the new anticoagulant and antiplatelet drugs

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Abstract In this review, we discuss the anesthetic implications of the new anticoagulant and antiplatelet drugs, focusing our discussion mainly on neuroaxial/regional anesthesia and central catheter placement issues. We offer practical recommendations for their use.

Keywords: Anticoagulant/antiplatelet drugs; Neuraxial anesthesia; Regional anesthesia

1. Introduction

The number of anticoagulant-treated patients who are scheduled for elective surgery is increasing continuously. Recent introduction of the new anticoagulant/antiplatelet agents may render the anesthetic management of these patients more challenging and complicated.

Specific questions for anesthetic management of patients receiving these drugs include possible discontinuation of the anticoagulant and/or antiplatelet medications, possible reversal of anticoagulants if surgery cannot be postponed, necessity for optimization, and/or normalization of coagulation status, whether clearance for surgery necessarily implies readiness for regional anesthesia and/or invasive monitoring (specifically pulmonary artery [PA] catheter placement) and other considerations.

Risks associated with compromised coagulation status may include increased perioperative blood loss [1–4], threat of epidural hematoma formation after neuraxial anesthesia [5,6], intrapulmonary hemorrhage after PA catheter placement [7], significant nasal bleeding after nasotracheal intubation, nasogastric tube placement [8-10], and others.

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2. A suggested classification of anticoagulant/antiplatelet medications according to their effects

A suggested classification of anticoagulant and antiplatelet drugs is based on a physiologic/pharmacological “site-of-action” approach and on some published data (Fig. 1) [11]. A detailed discussion regarding thrombolytics, which are used for treatment of acute myocardial infarction (MI) and pulmonary embolism (PE), is beyond the scope of this review.

3. Antiplatelet drugs

Antiplatelet drugs, although not true anticoagulants, exert their action on various aspects of platelet function, the most important of which is vascular wall adhesion. This group includes aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs); clopidogrel (an adenosine diphosphate receptor antagonist); dipyridamole (a phosphodiesterase inhibitor); and abciximab, epifibatide, and tirofiban (the glycoprotein [GP] IIb/IIIa receptor antagonists) [12].

Aspirin irreversibly inhibits prostaglandin-H synthetase (cyclooxygenase-1 or COX-1) in platelets and megakaryocytes, thereby blocking formation of thromboxane A2 (a potent vasoconstrictor and platelet aggregant). Because platelets cannot regenerate cyclooxygenase, the antithrombotic effect of aspirin remains for the lifespan of the platelets (8-10 days). There is a dose effect with low-dose aspirin (60-325 mg/d), which inhibits platelet COX-1 [13,14], whereas larger doses (1.5-2 g/d) also inhibit the production of prostacyclin by the vascular endothelial cells [14]. Aspirin is associated with a 60% to 70% increase in nonfatal extracranial hemorrhage (mostly from the gastrointestinal tract), with an incidence of one to two per 1,000 patients treated per year [15,16]. The risk of bleeding does not depend significantly on different aspirin daily doses or formulations (plain, enteric-coated, or buffered aspirin) [15,16].

Although only few data on the anesthetic implications of ticlopidine and clopidogrel are available [5], these drugs may increase the risk of spinal hematoma [6] formation after neuraxial anesthesia procedures. Thus, before the procedure, it is recommended that these drugs be discontinued for a period of 14 days for ticlopidine and 7 days for clopidogrel [5]. However, in one earlier report, no patient developed spinal hematoma or other postoperative neurologic deficits [17]. We were unable to find any data regarding anesthesia-related complications in patients receiving dipyridamole.

The GP IIb/IIIa receptor antagonists abciximab, epifibatide, and tirofiban have been approved for clinical use by the US Food and Drug Administration (FDA) [18]. These GP IIb/IIIa inhibitors are used mainly in the management of patients with recent MI and for those who undergo percutaneous coronary artery (PTCA) interventions [19-23], emergency CABG surgery [24-26], and treatment of acute ischemic stroke [27]. A bolus dose of abciximab causes a rapid interruption of the platelet aggregation process. Abciximab (and epifibatide) may prolong the activated clotting time (ACT) [28,29], almost to the same extent as heparin does in doses up to 100 IU/kg, although it remains unknown whether the ACT-prolonging effect of abciximab is clinically equivalent to that of heparin [21,30]. Abciximab causes pseudothrombocytopenia [30,31] and delayed immunogenic thrombocytopenia [32,33]. In a

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Fig. 1  Suggested classification of anticoagulant and antiplatelet drugs. ADP = adenosine diphosphate.
multicenter study [34], abciximab was shown to be safe for short-term use and also for readministration. No patient experienced any anaphylactic, allergic, or other hypersensitivity reactions attributable to abciximab [34].

Tirofiban possesses very similar features to those of abciximab, with a significantly shorter duration of action—4 to 8 hours—versus the 48-hour duration of action for abciximab [35].

Treatment with the GP IIb/IIIa inhibitors may increase the risk of bleeding complications, with potential fatal outcome. In a review of mortality in 450 cases [36], 44% of these deaths were definitely or probably related to the use of these drugs. Of those 450 fatal outcome cases, 103 (23%) were associated with eptifibatide, 143 (32%) with tirofiban, and 207 (46%) with abciximab treatment [36].

The following precautions regarding the anesthetic management of patients receiving antiplatelet medication are recommended [5,15,37]:

— There are no universally accepted coagulation tests, including bleeding time, which could guide antiplatelet therapy. Careful clinical assessment and detection of conditions such as history of easy bruising or excessive bleeding are crucial. Female gender and advanced age are identified as risk factors of excessive activity of antiplatelet therapy.

— Nonsteroidal antiinflammatory drugs appear unlikely to aggravate the risk of spinal hematoma formation after epidural or spinal anesthesia. The use of NSAIDs alone does not create a level of risk that might prevent the use of neuraxial blocks.

— The actual risk of spinal hematoma in patients receiving ticlopidine or clopidogrel or the GP IIb/IIIa antagonists is unknown. Consensus management is based on labeling precautions and surgical and interventional cardiologic/radiologic experience.

— The suggested time interval between discontinuation of therapy and neuraxial block is 14 days for ticlopidine and 7 days for clopidogrel.

— Platelet GP IIb/IIIa receptor inhibitors exert a more profound effect on platelet aggregation. After their administration, the time to restoration of normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for both eptifibatide and tirofiban. Neuraxial techniques should be avoided until platelet function is fully recovered. If these drugs are administered in the postoperative period, the patient should be carefully monitored neurologically [5,15].

4. Defibrinogenating drugs: ancrod

Ancrod is a defibrinogenating, proteolytic enzyme with selective substrate specificity to fibrinogen. It cleaves to, and therefore inactivates, a significant part of circulating plasma fibrinogen, specifically fibrinopeptides from the A-α chain of fibrinogen. The resulting fibrin monomers (known as ancrod-fibrin) cannot be cross-linked by factor XIIIa and form unstable, soluble chains. The selective action of ancrod on the A-α chain of fibrinogen explains the increased susceptibility of ancrod-fibrin to lysis by plasmin and its rapid clearance from the circulation by the reticuloendothelial system. It also indirectly inhibits aggregation, adhesion, and release of thrombocytes mediated through the action of a fibrinogen degradation product (Viprinex [ancrod] package insert; Knoll AG [Abbott Laboratories], Ludwigshafen, Germany) [38].

Ancrod administration is followed by a rapid decrease in plasma fibrinogen within minutes, which remains low for the duration of its use. Once ancrod is withdrawn, plasma fibrinogen returns to hemostatic levels within 24 to 48 hours and to pretreatment levels within days. Activation of fibrinolysis after ancrod administration is thought to be rapid, and it may occur before levels of fibrinogen are measurably reduced. The limited cleavage of plasma fibrinogen to ancrod-fibrin during the first hour of ancrod administration may be sufficient to initialize the process and induce fibrinolysis (Viprinex [ancrod] package insert; Knoll AG [Abbott Laboratories], Ludwigshafen, Germany) [38].

The limited pharmacological activity of ancrod may explain the low incidence of hemorrhagic complications, in contrast with higher complication rates of standard anticoagulants and thrombolytics (eg, streptokinase, urokinase) [39-41]. Ancrod is a comparable alternative to heparin in various clinical settings such as vascular surgery [42], thromboembolism treatment/prophylaxis in patients with multiple trauma [43], cardiopulmonary bypass (CPB) procedures [44,45], and treatment of acute ischemic stroke [27].

We were unable to find any controlled studies or case reports regarding anesthesia-related risks or complications encountered after neuraxial blocks were performed in patients treated with ancrod. The lack of serious bleeding complications has been mentioned only once [42]. Nevertheless, it would be prudent to avoid neuraxial or plexus blocks in patients receiving ancrod.

5. Heparins

5.1. Low-molecular-weight heparins

Low-molecular-weight heparins (LMWHs), fragments approximately one third the size of the parent compound, are produced by enzymatic or chemically controlled hydrolysis of unfractionated heparin molecules. The average molecular weight of these LMWHs typically ranges from

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4,000 to 6,500 Daltons (DA), as opposed to the unfractionated heparins, which have an average molecular weight of 15,000 DA [46]. Molecules of LMWHs have very similar nated heparins, which have an average molecular weight of 4,000 to 6,500 Daltons (DA), as opposed to the unfractionated heparins. Low-molecular-weight heparins exert their effect by inhibiting factor Xa and augmenting tissue-factor-pathway inhibitor, but they minimally affect thrombin or factor IIa. Thus, the activated partial thromboplastin time (aPTT), a measure of antithrombin (antifactor IIa) activity, is not useful in measuring the activity of LMWHs, which requires instead a specific anti-Xa assay [47].

In addition to having lower antithrombin activity than unfractionated heparin, LMWHs bind less to plasma proteins, endothelium, and macrophages, permitting greater bioavailability and little interpatient and intrapatient variability in response to a given dosage. Clinical trials have confirmed that effective antithrombotic activity can be consistently achieved by calculating dosages based on body weight, without the need for laboratory monitoring [48].

Because these agents are eliminated primarily through the kidneys, accumulation of antifactor Xa activity may occur in patients with chronic renal insufficiency [49-51]. The LMWHs also appear to be associated with less bleeding and a decreased frequency of heparin-induced thrombocytopenia, as a result of their lower affinity for platelets and von Willebrand factor [52].

The LMWHs currently available in the United States are enoxaparin, dalteparin, and ardeparin, whereas nadroparin, tinzaparin, and reviparin are marketed elsewhere. Enoxaparin was recently labeled by the FDA for outpatient treatment of deep vein thrombosis (DVT) and also may be used for this purpose in inpatients with or without PE. Enoxaparin and dalteparin are commonly used in the management of acute coronary syndromes [53,54].

The LMWHs are prepared using different methods of depolymerization, resulting in distinct molecular weights (4,000-5,500 DA). Their relative effects on factor Xa and thrombin imply that these agents are not necessarily therapeutically interchangeable, although their pharmacologic and clinical characteristics are similar [46,47,54].

Several meta-analyses have shown that LMWHs are associated with statistically higher clinical efficacy compared with that of unfractionated heparins in the treatment of established DVT. Unlike the newer anticoagulant alternatives, unfractionated heparins paradoxically stimulate platelet aggregation, which may further promote clot formation [55]. The results showed a statistically significant reduction in thrombus size, recurrent venous thromboembolism, major bleeding events, and pooled long-term mortality rate [55]. Although the lower mortality rates observed in these trials were mostly attributable to a subgroup of patients with cancer, the data may indicate greater efficacy of LMWHs in this high-risk population [46,47]. The LMWHs cannot be neutralized by protamine [55].

Bemiparin, an LMWH, has shown efficacy in the prevention of venous thromboembolism and in the treatment of established DVT in a number of controlled clinical trials. It can be initiated preoperatively and postoperatively, with relatively lower incidence of bleeding complications [56] than the other LMWHs.

We suggest that patients who receive an LMWH for perioperative DVT prophylaxis be cautiously, if at all, considered as candidates for epidural or spinal anesthesia because of the theoretically greater risk of epidural hematoma. To date, the estimated incidence of this complication is less than 1:150,000 for epidural anesthetics and less than 1:220,000 for spinal anesthetics [57]. Precautions believed to be helpful in preventing occurrence of spinal hematoma in selected cases as follows: one-attempt needle placement, immediate needle withdrawal in cases of appearance of minimal amount of blood in the hub of the needle, and use of pencil-point needles only [58-61].

For patients who receive preoperative LMWH therapy, general recommendations are as follows [5]:

— Patients receiving preoperative LMWH thromboprophylaxis can be assumed to have altered coagulation. In these patients, needle placement should be delayed for at least 10 to 12 hours after the last LMWH dose.
— In patients receiving higher doses of LMWH such as enoxaparin, 1 to 1.5 mg/kg every 12 hours or daily; dalteparin, 120 U/kg every 12 hours or 200 U/kg daily; or tinzaparin, 175 U/kg daily, needle instrumentation should be postponed for at least 24 hours.
— All neuraxial techniques should be avoided in patients who received a dose of LMWH two hours preoperatively.
— Patients receiving LMWHs postoperatively may safely undergo single-injection and continuous catheter techniques. For those patients receiving a twice-daily regimen, whose first dose of LMWH is administered two hours after catheter removal, the epidural catheter may be left indwelling overnight and removed the following day. For patients receiving a single daily dose regimen, the catheter should be removed a minimum of 10 to 12 hours after the last dose of LMWH, and subsequent doses should be administered a minimum of two hours after catheter removal.

6. Direct thrombin inhibitors

6.1. Leech proteins

Hirudin, the most potent thrombin inhibitor [62], is a polypeptide produced by the salivary glands of the medical leech (Hirudo medicinalis). In 1976, the primary chemical structure of hirudin was established [63-65].

Hirudin and, to a lesser extent, polyethylene-glycol-coupled hirudin (PEG-hirudin) have been used in many
clinical trials. Hirudin is more effective than LMWHs in preventing DVT after total hip replacement surgery [66]. The PEG-hirudin was used successfully as a single anticoagulant in dialysis patients with end-stage renal disease [64]. In addition, PEG-hirudin can maintain a residual anticoagulant effect between dialysis sessions, which may prevent thrombotic vascular access complications [67].

Lepirudin (Refludan; Bayer Healthcare, Wayne, NJ) was the first direct thrombin inhibitor to be approved by the FDA in 1998 for anticoagulation in patients with heparin-induced thrombocytopenia (HIT) and heparin-induced thrombocytopenia and thrombosis syndrome (HITTS). Lepirudin is important because it is one of the alternatives, such as hirudin [68,69], which is available for CPB in patients with HIT/HITTS and positive antibodies for heparin [67,70-72]. Lepirudin binds to two sites of thrombin, producing irreversible thrombin-lepirudin complexes that are excreted by the kidneys. Lepirudin is a highly potent and specific direct inhibitor of both circulating and clot-bound thrombin [68]. Lepirudin is administered as loading dose of 0.4 mg/kg given for 15 to 20 seconds, immediately followed by infusion of 0.15 mg/kg per hour as long as clinically indicated.

Benefits of lepirudin include immediate onset, a relatively short elimination half-life, and lack of reported cross-reaction with heparin-induced antibodies [73]. However, lepirudin and another synthetic leech protein, bivalirudin, possess potent immunogenic features [74]. Lepirudin recently was linked to at least 9 cases of severe anaphylaxis, four of which had a fatal outcome [72,75]. Formation of IgG antihirudin antibodies usually takes 7 to 10 days and was observed in 40% of HIT patients receiving lepirudin. This condition may increase the anticoagulant effect of lepirudin possibly because of delayed renal elimination of active lepirudin-antihirudin complexes [75]. Monitoring of lepirudin therapy is challenging because there is a poor link between prolongation of ACT and partial thromboplastin time (pTT) values and the relatively high lepirudin concentrations during CPB. Ecarin clotting time is designed to monitor the anticoagulant effects of lepirudin, hirudin, and argatroban [76], and with a short measuring time, it correlates well with lepirudin serum concentration and is not influenced by the aprotinin [76-79].

The most frequently occurring adverse events with lepirudin were anaphylactic reactions [80] and hemorrhagic complications—hematomas, hematuria, bleeding from puncture sites and wounds, and occasionally, epistaxis [81]. One of the main disadvantages of lepirudin is lack of a known antidote [81], and therefore, immediate reversal is not possible. Lepirudin is eliminated through the kidneys mainly unchanged (48%), so it should be used with caution in patients with renal failure because of the potential for a prolonged effect. A much longer effect of lepirudin is expected in this category of patients. The usual half-life of lepirudin is 1.3 hours; in patients with severe renal function impairment (renal blood flow ≤15 mL/min), its half-life may reach two days [65].

A new direct thrombin inhibitor (DTI) approved by the FDA in 2000 is bivalirudin [82-84], a synthetic analog of hirudin, which is actually fragmented lepirudin. Unlike hirudin, bivalirudin produces only transient inhibition of the active site of thrombin [85]. The main advantage of the drug is a much shorter half-life (25 min), and renal excretion is not a major route of its clearance. Instead, it is likely that bivalirudin is degraded by endogenous peptidases, and consequently, it may be safer than hirudin in patients with renal impairment [65,86].

The drug was approved by the FDA for use together with aspirin in patients with coronary artery disease or acute MI and undergoing PTCA [87-89]. Bivalirudin produces a 50% reduction in major bleeding compared with heparin [65,90,91].

Several studies have shown that bivalirudin is highly effective, associated with fewer major complications, and is by far more convenient for clinical use than hirudin in patients with HIT who are undergoing CPB [92]. All of these features render bivalirudin an alternative to heparin during cardiac surgery [90,93-95].

Ecarin clotting time is a useful assay for monitoring bivalirudin activity, enabling precise control of the drug dosage [90,96,97].

Because hirudin, lepirudin, and bivalirudin are used almost exclusively in special settings such as PTCA or cardiac surgery in patients with HIT, where both neuraxial and peripheral techniques are unlikely to be used, no recommendations regarding these techniques are currently available. We suggest that these drugs be avoided until the effect has dissipated, or has been documented to have dissipated.

7. Synthetic direct thrombin inhibitors

7.1. Argatroban

Argatroban is a synthetic, reversible DTI. The drug is currently used for the prophylaxis and treatment of thrombosis in patients with HIT/HITTS [98-101]. Argatroban exerts its anticoagulant effects by inhibiting thrombin-induced or thrombin-catalyzed reactions, including fibrin formation, activation of coagulation factors (V, VIII, XIII), activation of protein C, and platelet aggregation [58,102]. Argatroban is capable of inhibiting the activity of both free and clot-associated thrombin [103]. Argatroban can delay the onset of platelet contractile force, but its strength decreases in a dose-dependent fashion during CPB [104].

Argatroban is metabolized mainly by the liver and excreted through biliary secretion. The elimination half-life of the drug is approximately 45 minutes [105,106]. The dosage of argatroban obviously should be decreased in patients with hepatic impairment, in whom the drug clearance is decreased and elimination half-life is prolonged [107].
Argatroban can be safely administered in patients with impaired renal function, and no dosage adjustment is necessary [108].

Anticoagulant effects associated with argatroban infusion correlate with increases in aPTT [108]. Although other global clot-based tests (eg, PT; international normalized ratio; thrombin time [TT]) are affected by argatroban, the therapeutic ranges for these tests have yet to be determined. However, ecarin clotting time, whereas being insensitive to heparins, is much more sensitive to DTIs such as argatroban and melagatran [79]. Argatroban has no significant pharmacokinetic interactions with warfarin. In another study [109], PT was prolonged comparably when argatroban was administered either alone or with warfarin.

There is no specific antidote to argatroban [81]. In clinical studies, at therapeutic levels, coagulation parameters generally return to baseline within two to four hours of discontinuation of the drug. Reversal of anticoagulant effect may take longer in patients with hepatic impairment [97,101].

Argatroban is now widely used in patients with HIT and its thrombotic complications [68,110-117]. Compared with lepirudin, argatroban is more effective and safer in the management of HIT [68] in patients undergoing CABG surgery [72,117-120], adult extracorporeal membrane oxygenation alone [121], CPB in infants [122] and children [123], and in patients with acute coronary syndromes [124]. There is one report of failure to achieve anticoagulation with argatroban during off-pump CABG surgery [125]. Argatroban has been tested successfully as an option for anticoagulation in dialysis-dependent patients [64].

7.2. Melagatran and ximelagatran

Ximelagatran, a precursor of melagatran, is a synthetic, active, site-directed thrombin inhibitor. These drugs have been in use for a while in the prophylaxis of venous thromboembolism and prevention of arterial thrombosis [126-133]. Unfortunately, both drugs are no longer FDA-approved and were withdrawn from the market because of their severe adverse effects, mainly cellular liver damage, with elevation of liver enzymes, and the development of subsequent liver failure [134,135].

8. Synthetic antithrombin III-dependent factor Xa inhibitors

8.1. Fondaparinux, idraparinux

Fondaparinux (Arixtra; GlaxoSmithKline, Philadelphia, PA) is the first of a new class of selective, indirect, antithrombin III-dependent factor Xa inhibitors, a completely synthetic pentasaccharide, with almost 100% bioavailability [136-138]. Fondaparinux has no effect on the rate of thrombin inhibition, no known effect on platelet function, and does not affect fibrinolytic activity or bleeding time [139,140]. It does produce a concentration-dependent prolongation of ACT, whereas ecarin clotting time and TT remain unaffected [141]. Its peak plasma level is obtained about two hours after subcutaneous injection. Its half-life is about 17 hours and is dose-dependent. Fondaparinux is eliminated exclusively by the kidneys and is contraindicated in patients with severe renal insufficiency. There is no antidote to either fondaparinux or idraparinux [84,139,142,143]. Fondaparinux is well tolerated by patients who are allergic to heparin and heparinoids, and it has no interaction with the immunologic mechanisms of HIT [144,145].

Fondaparinux has been used successfully for treatment and prophylaxis of thromboembolic complications of any kind (primarily DVT) [85,146-150], especially after major orthopedic surgery (ie, total hip replacement and major knee surgery) [139,142-153]. Fondaparinux has been studied in the treatment of unstable angina and other acute coronary syndromes, but it has not yet been approved for this indication [139,143,154].

Idraparinux, a selective, long-acting factor Xa inhibitor, basically shares many of the properties of fondaparinux, especially a long half-life. Idraparinux is useful in the treatment of DVT and PE, though its exact indications have yet to be finally established [155]. Some studies have shown significant increases in liver enzymes during treatment with idraparinux. Plasma levels of liver enzymes returned to initial levels quickly as soon as the medication was stopped [156]. Recombinant factor VIIa may effectively reverse the anticoagulant effect of idraparinux [157]. Idraparinux is effective in the treatment of DVT in patients receiving 2.5 mg of subcutaneous injection once a week, and its efficacy is similar to that of heparin plus a vitamin K antagonist [158].

There are few data regarding anesthetic complications in patients receiving DTIs or synthetic anti-III inhibitors. We found no reports of spinal hematoma after neuraxial anesthesia in this group of patients; however, spontaneous intracranial bleeding has been reported [5]. It seems wise to refrain from performing neuraxial anesthesia in patients receiving these drugs.

9. Conclusion

The main purpose of this review was to discuss potential neuroaxial and regional anesthesia-related issues in patients receiving new anticoagulant/antiplatelet drugs. The growing number of newly introduced anticoagulant/antiplatelet drugs necessitates increased awareness of the possible complications of their use. Increased blood loss and coagulation defects are the immediate problems to be considered by the anesthesiologist. Use of neuraxial and other regional techniques in patients receiving new antiplatelet drugs, DTIs, and specific factor blockers may lead to spinal hematoma formation, with consequent neurologic deficit.
References

Anesthesia and new anticoagulants


References: