New Anticoagulants and Emerging Trends in Regional Anesthesia

HARENDRA ARORA, MD
Professor, Anesthesiology
Program Director, Anesthesiology Residency
Section Head, Vascular and Transplant Anesthesia
UNC School of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

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The use of anticoagulant and antiplatelet agents has been increasing, primarily as a result of improved life expectancy, the aging population, prevalence of cardiovascular disease, and expansion of indications for more potent anticoagulants.

Traditionally, the incidence of neurologic complications as a result of hemorrhagic complications from neuraxial anesthesia has been estimated to be approximately 1 in 150,000 for epidurals and 1 in 220,000 for spinal anesthetics. This risk may be higher in certain high-risk patients. For example, in one epidemiological study from Sweden, the risk for spinal hematoma after epidural analgesia was estimated to be 1 in 3,600 in elderly women undergoing knee arthroplasty compared with 1 in 200,000 in women undergoing childbirth. Additionally, the expanded use of newer, more potent anticoagulants may further add to the risk for hemorrhagic complications after regional anesthesia.

Since the release of the third edition of the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines to assist with decision making for regional anesthesia in patients treated with anticoagulants, a number of new oral anticoagulants (NOACs) have been approved by the FDA. It is expected that the fourth edition of the ASRA guidelines, which are likely to be published soon, will address regional anesthesia for patients treated with NOACs. Most recently ASRA, The European Society of Regional Anaesthesia & Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain published guidelines for interventional spine and pain procedures in patients taking antiplatelet and anticoagulation medications.

It is expected that the fourth edition of the ASRA guidelines for regional anesthesia will be somewhat similar to the recently published interventional pain
Risk Factors for Hemorrhagic Complications After Regional Anesthesia

Bleeding after neuraxial techniques most commonly occurs in the epidural space from injury to the epidural venous plexus. The most frequent risk factor associated with hemorrhagic complications following neuraxial anesthesia is concomitant administration of anticoagulants. In their review of the literature between 1906 and 1994, Vandermeulen et al reported 61 cases of spinal hematomas after neuraxial procedures. Eighty-seven percent of these patients had an associated hemostatic abnormality or traumatic placement of an epidural or spinal anesthesia. In about one-third of the patients, more than one risk factor was present. Partial or complete neurologic recovery, which was reported in only 38% of the patients, was more likely in patients who underwent laminectomy within 8 hours of the onset of neurologic symptoms.

Moen et al, in their review of 1,260,000 spinal and 450,000 epidural blocks performed in Sweden over a 10-year period, identified coagulopathy (preexisting or acquired), spinal stenosis, female gender, and epidural technique (as opposed to spinal anesthetic) as risk factors for hemorrhagic complications from neuraxial anesthesia.

Among the anticoagulants, neuraxial bleeding complications have been reported most commonly with the use of unfractionated heparin or low-molecular-weight heparin (LMWH). Of note, LMWH had been concurrently used extensively with spinal and epidural anesthesia in Europe for over 2 decades before its approval in the United States, in 1993. The safety of LMWH in combination with neuraxial blockade was also well documented in Europe. However, in the first 5 years after the introduction of LMWH in the United States, more than 40 spinal hematomas were reported through the FDA’s MedWatch system.

The single most important risk factor identified during review of these cases was the dosing schedule of LMWH, with once-daily dosing prevalent in Europe and twice-daily dosing prevalent in the United States. As a result, ASRA recommended against indwelling epidural catheters in patients receiving a twice-daily dosage of LMWH. Additionally, several other factors were also identified during the review of these cases that might have contributed to the increased risk for spinal hematomas (Table).

Table. Risk Factors Associated With Spinal Hematoma in Patients Receiving LMWH

<table>
<thead>
<tr>
<th>Risk Factor</th>
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</thead>
<tbody>
<tr>
<td>Concomitant antiplatelet or anticoagulant agents</td>
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<tr>
<td>Early postoperative LMWH administration</td>
</tr>
<tr>
<td>Elderly patients</td>
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<tr>
<td>Epidural technique (as opposed to single-shot spinal)</td>
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<tr>
<td>Female sex</td>
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<tr>
<td>Immediate preoperative LMWH administration</td>
</tr>
<tr>
<td>Indwelling epidural catheter</td>
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<tr>
<td>Renal insufficiency</td>
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<tr>
<td>Spinal stenosis</td>
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<tr>
<td>Traumatic needle placement</td>
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<tr>
<td>Twice-daily LMWH administration (as opposed to once-daily LMWH regimen)</td>
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Consequently, the majority of recommendations from various American and European societies are based on large case series, case reports, expert opinion, manufacturers’ drug labels, and the pharmacology of the anticoagulant involved.

These recommendations typically include a minimum time interval between the last dose of the anticoagulant and placement of neuraxial block as well as the minimum time from insertion of neuraxial block and the next dose of anticoagulant agent. Of note, there are some differences in recommendations between various societies.

Because there is limited clinical experience with newer anticoagulants, some experts have proposed timing of neuraxial procedures according to a drug’s elimination half-life. For example, Rosencher et al proposed insertion and subsequent withdrawal of a neuraxial catheter with an interval of at least 2 elimination half-lives for any given anticoagulant. This is based on the assumption that only 30% to 40% of the function of coagulation factors is required for hemostasis. This has been the basis of the European and Scandinavian guidelines, which follow 2 half-life intervals between drug discontinuation and neuraxial intervention.

It is important to understand the relationship between elapsed half-lives and the remaining activity of a given drug. After 1 to 6 half-lives, the percentage of drug remaining is 50%, 25%, 12.5%, 6.25%, 3.12%, and 1.6%, respectively. Therefore, at 5 half-lives only 3% of a given drug remains. This is the justification for the recent ASRA guidelines for interventional pain procedures. Moreover, when new anticoagulants are studied, most undergo trials in healthy individuals as opposed to non-research patient populations that are likely to have minimal prospective trials of the use of neuraxial techniques in patients receiving antithrombotic agents.

Guidelines for Regional Anesthesia In Patients Treated With Anticoagulants

Because spinal hematomas are rare, it is difficult to study enough patients to determine the risk associated with individual antithrombotic agents. As such, there are minimal prospective trials of the use of neuraxial techniques in patients receiving antithrombotic agents.
other multiple confounders (elderly patients, renal compromise, anatomical spinal abnormalities, concomitant anticoagulants, etc).

Benzon et al prefer the approach whereby the risk for thrombotic complications is weighed in order to determine the time interval for drug discontinuation and subsequent neuraxial procedure. They proposed an interval of 5 elimination half-lives between drug discontinuation and neuraxial procedures in patients at low thrombotic risk, as assessed by CHA₂DS₂-VASC score. On the other hand, in patients at high risk for venous thromboembolism (VTE) or stroke, these authors recommended an interval of 2 to 3 half-lives.

Because NOACs are eliminated through the kidneys, adjustments should also be made for patients with reduced creatinine clearance. The 2015 ASRA guidelines for interventional pain procedures recommend an interval equal to 5 half-lives (4 days) between drug discontinuation and interventional pain procedure, to allow for the majority of the drug to be cleared.

When it comes to resuming the anticoagulant drug after neuraxial intervention, including epidural catheter removal, the Scandinavian guidelines recommend 8 hours minus the time for the drug to reach peak effect. This is based on the assumption that it takes approximately 8 hours for a platelet plug to form a stable clot. This has been demonstrated through serial MRI after epidural blood patches that showed the clot to be resolved by 7 hours. It has also been shown that thrombolytics are more effective when given within 3 hours after the onset of stroke.

Others recommend a longer duration between neuraxial intervention and resumption of the anticoagulant agent. For example, Liew and Douketis recommended a minimum of 24 hours in patients with low bleeding risk and 48 hours in those with a high bleeding risk, before resuming NOACs. Baron et al recommended a 48-hour interval for all patients, whereas Connolly and Spyropoulos recommended a 24-hour interval, but at half the usual dose.

The 2015 ASRA guidelines for interventional pain procedures recommend an interval for 72 hours for resumption of NOACs after neuraxial intervention. In case the risk for VTE is considered to be very high, a 12-hour interval, at half the baseline dose, may be considered. It is important that these decisions are made in consultation with the treating physician(s) on the basis of the overall risk–benefit ratio.

New Anticoagulants

**Fondaparinux**

**Relevant Pharmacology**

Fondaparinux (Arixtra, GlaxoSmithKline) is a synthetic indirect Xa inhibitor with potent anticoagulant activity. It is indicated for VTE prophylaxis after major orthopedic surgery as well as for treatment of pulmonary embolism. Fondaparinux has been shown to be superior to LMWH for VTE prophylaxis following total hip and knee arthroplasties.

After administration, maximum drug concentration is reached within 1.7 hours. Because the half-life of fondaparinux approaches 17 to 21 hours, it allows for a twice-daily dosing schedule. Prophylactic therapy with fondaparinux is typically 2.5 mg once daily, started 6 hours postoperatively. Because fondaparinux has significant renal clearance (77% of the administered drug), the manufacturer recommends dose adjustment in patients with moderate renal insufficiency (1.5 mg rather than 2.5 mg). It is contraindicated in patients with severe renal insufficiency.

**Monitoring**

Even though the effect of fondaparinux can be monitored with anti-Xa activity, such monitoring is not required.

**Background Evidence**

As is the case with most NOACs, the actual risk for spinal hematoma with fondaparinux is unknown due to a lack of published data. The 2015 ASRA guidelines recommended against the use of indwelling epidural catheters in patients on fondaparinux therapy. With regard to single-shot spinals, the recommendation was to follow strict conditions, as was done during the initial clinical trials (atraumatic needle placement and single-needle pass).

The EXPERT study, which included 1,631 patients undergoing continuous neuraxial or deep peripheral blocks in conjunction with fondaparinux, reported no serious hemorrhagic complications. The catheters were removed 36 hours after the last dose of fondaparinux, which only allowed an interval equal to 2 half-lives between drug discontinuation and catheter removal. Even though there were no spinal hematoma cases, this study lacked sufficient power to make firm conclusions given the low incidence of this complication.

The 2015 ASRA guidelines for interventional pain procedures recommend an interval equal to 5 half-lives (4 days) between drug discontinuation and an interventional pain procedure to allow for the majority of the drug to be cleared. These guidelines recommend delaying resumption of fondaparinux 24 hours after the intervention, to account for its short onset of effect.

**Recommendations**

- Time interval for which fondaparinux needs to be discontinued before neuraxial puncture/catheter manipulation or removal: 4 days.
- Time interval when fondaparinux can be restarted after neuraxial puncture/catheter manipulation or removal: 24 hours.

**Rivaroxaban**

**Relevant Pharmacology**

Rivaroxaban (Xarelto, Janssen) is a direct-acting factor Xa inhibitor. It is indicated for VTE prophylaxis during orthopedic surgery as well as for stroke prevention from nonvalvular atrial fibrillation. Rivaroxaban is shown to be as effective as LMWH for VTE.
prophylaxis. The typical dose administered is 10 mg of rivaroxaban, 6 to 8 hours after surgery. Time to peak plasma concentrations has been observed between 2.5 and 4 hours, whereas the half-life of rivaroxaban is 5 to 9 hours. Rivaroxaban is cleared through the kidneys (33%) and fecal/biliary route (33%), with the remaining one-third of the drug metabolized to inactive metabolites.

Because rivaroxaban is partly metabolized by the liver, it should be avoided in patients with severe liver disease. Because only one-third of the drug is eliminated through the kidneys, the likelihood of significant accumulation is small, although caution is advised in elderly patients with worsening renal function, when its half-life can be prolonged to 11 to 13 hours.

Monitoring
Rivaroxaban prolongs the prothrombin time (PT) in a dose-dependent manner, but until further data are available, monitoring with PT is not recommended. There is no specific antidote available.

Background Evidence
As is the case with most NOACs, the actual risk for spinal hematoma with rivaroxaban is unknown due to limited published data. Four RECORD (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism) studies assessed the efficacy and safety profile of DVT prophylaxis after knee or hip replacement surgery with rivaroxaban. In these trials, there were no cases of spinal hematomas in the 1,141 patients who received rivaroxaban along with neuraxial anesthesia. Epidural catheters were removed after an interval of at least 2 half-lives after the last dose of rivaroxaban, and the subsequent dose was administered 4 to 6 hours after catheter removal.

No conclusions can be made about the safety of the 2 half-life interval, despite the fact that there were no cases of spinal hematomas, given the small sample size. The Scandinavian and European society guidelines recommend an interval of 2 half-lives between the last dose of rivaroxaban and epidural catheter removal.

The 2015 ASRA guidelines for interventional pain procedures recommend an interval equal to 5 half-lives (3 days) between drug discontinuation and neuraxial procedures, to allow for the majority of the drug to be cleared. These guidelines recommend delaying resumption of rivaroxaban 24 hours after the intervention to account for its short onset of effect (2.5-4 hours), unless the VTE risk is high.

Recommendations

• Time interval for which rivaroxaban needs to be discontinued before neuraxial puncture/catheter manipulation or removal: 3 days.
• Time interval when rivaroxaban can be restarted after neuraxial puncture/catheter manipulation or removal: 24 hours. If the risk for VTE is considered to be high, then half the usual drug dose can be administered 12 hours after the procedure.

Apixaban

Relevant Pharmacology
Apixaban (Eliquis, Bristol-Myers Squibb) is an orally administered, reversible, direct factor Xa inhibitor, similar to rivaroxaban. Its bioavailability, when administered orally, ranges from 51% to 85%, and peak concentrations are achieved within 1 to 2 hours. When apixaban is administered twice daily, steady state is reached in about 3 days. Its half-life is between 10 and 15 hours, and elimination occurs through multiple pathways, with 25% of the drug excreted by the kidneys and 75% by liver and biliary metabolism, as well as intestinal excretion.

Apixaban has been shown to be as effective as LMWH for the treatment of acute VTE, with significantly less bleeding risk. Apixaban has also been shown to be superior to aspirin or warfarin in patients treated for stroke prevention.

Monitoring
Unlike rivaroxaban, apixaban has little effect on the PT. Anti-Xa assay seems to correlate well with the anti-coagulant activity of apixaban.

Background Evidence
As is the case with other NOACs, the actual risk for spinal hematoma with apixaban is unknown due to a lack of published data. The recommendations are based on the pharmacologic profile and half-life of the drug and its clearance. The European society guidelines recommend waiting 2 half-lives (26-30 hours) between drug discontinuation and neuraxial procedures or catheter removal. European guidelines allow for drug resumption 4 to 6 hours after neuraxial procedures.

As with other NOACs, the 2015 ASRA guidelines for interventional pain procedures recommend an interval equal to 5 half-lives (3-5 days) between drug discontinuation and neuraxial procedures, to allow for the majority of the drug to be cleared. Because apixaban has a wide variability in its pharmacokinetics (half-life can vary significantly), a range of 3 to 5 days has been recommended as an appropriate time interval before neuraxial intervention. These guidelines recommend delaying resumption of apixaban 24 hours after the intervention, to account for its short onset of effect (1-2 hours), unless the VTE risk is high.

Recommendations

• Time interval for which apixaban needs to be discontinued before neuraxial puncture/catheter manipulation or removal: 3 to 5 days.
• Time interval when apixaban can be restarted after neuraxial puncture/catheter manipulation or removal: 24 hours. If the risk for VTE is considered to be high, then half the usual drug dose can be administered 12 hours after the procedure.

Dabigatran

Relevant Pharmacology
Dabigatran (Pradaxa, Boehringer Ingelheim) is a prodrug that is hydrolyzed by esterases in the stomach to the active drug dabigatran, which is a reversible monovalent direct thrombin inhibitor. Peak plasma
concentrations are achieved within 1.5 to 3 hours after oral intake. The half-life of dabigatran ranges between 14 and 17 hours and is minimally affected by sex, body weight, obesity, or ethnic origin. Because dabigatran is cleared mostly through the kidneys (80%), its elimination half-life is doubled from 14 to 28 hours in patients with end-stage renal disease.

Dabigatran has been shown to be effective in stroke prevention in patients with nonvalvular atrial fibrillation. However, it is not currently approved for VTE prophylaxis in the United States. Dabigatran is approved for VTE prophylaxis in Europe and Canada.

**Monitoring**

Thrombin time is a highly sensitive test that has been used to detect the anticoagulant effects of dabigatran. However, thrombin time is not useful in quantifying the effect because it lacks a linear correlation with dabigatran drug concentrations. The ecarin clotting time, on the other hand, has a linear correlation with dabigatran concentrations and is considered to be the most sensitive assay for dabigatran.

Although activated partial thromboplastin time is prolonged after dabigatran administration, it lacks a linear correlation. The PT is the least sensitive test.

**Background Evidence**

As is the case with other NOACs, the actual risk for spinal hematoma with dabigatran is unknown due to a lack of published data. In the initial studies with dabigatran, neuraxial blockade was performed in approximately 70% of the patients, but all epidural catheters were removed at least 4 to 6 hours before the first dose. The manufacturer advises against the use of dabigatran in the presence of neuraxial blockade. The European society guidelines also recommend against neuraxial interventions in the presence of dabigatran. The 2015 ASRA guidelines for interventional pain procedures recommend an interval equal to 5 half-lives (4-5 days) between drug discontinuation and neuraxial procedures to allow the majority of the drug to be cleared.

**Recommendations**

- Time interval for which dabigatran needs to be discontinued before neuraxial puncture/catheter manipulation or removal: 4 to 5 days.
- In patients with end-stage renal disease, because the half-life of dabigatran is around 28 hours, it is advised to wait 6 days before neuraxial intervention.
- Time interval when dabigatran can be restarted after neuraxial puncture/catheter manipulation or removal: 24 hours. If the risk for VTE is considered to be high, then half the usual drug dose can be administered 12 hours after the procedure.

**General Strategy for Management of Patients Taking Anticoagulants**

Anticoagulants and antiplatelet agents pose a significant challenge in patients who are being considered as candidates for regional anesthesia. Newer anticoagulants further add to the risk, given the paucity of available data on these agents. Most of the recommendations on newer agents are based on drug pharmacokinetics. Below are some general principles to assist in decision making when considering regional anesthesia in patients who are on concurrent anticoagulants:

- Weigh the risks and benefits of regional anesthesia for the individual patient after careful review of the patient’s history and physical examination, including family history of bleeding disorders.
- Coagulation tests should be obtained when appropriate, on the basis of the history and physical examination and the anticoagulant agent being used.
- Optimize the patient’s coagulation status at the time of regional anesthesia, and monitor the level of anticoagulation carefully while an epidural catheter is maintained.
- Single-shot spinal is considered to be safer than use of an indwelling epidural catheter.
- Concomitant administration of medications that affect hemostasis, such as antiplatelet agents, nonsteroidal anti-inflammatory drugs, and so forth, pose additional risk for hemorrhagic complications from regional anesthesia and should be considered when weighing the risks.
- Weigh the risks of drug discontinuation (thrombosis risk) and continuation (bleeding risk). It is advised to practice shared decision making with the patient’s treating physician(s) with regard to anticoagulant/antiplatelet drug discontinuation and resumption in the perioperative period.
- Understand drug pharmacology in the context of the specific patient, including drug elimination and onset times of the anticoagulant being used, in order to determine appropriate timing of drug discontinuation and resumption with regard to regional anesthesia.
- Where appropriate, use lower concentrations of local anesthetic in order to allow for close neurologic monitoring, especially in patients with indwell- ing epidural catheters.

**Conclusion**

The use of anticoagulant and antiplatelet agents has been increasing, primarily as a result of improved life expectancy, the aging population, prevalence of cardiovascular disease, and expansion of indications for more potent, newer anticoagulants. New guidelines are emerging for safe perioperative management of patients on anticoagulant/antiplatelet agents with regard to regional anesthesia. For the NOACs, the knowledge of drug pharmacology is the basis for establishing a safe time interval for performance of regional anesthesia.

It is important that the decisions to discontinue and restart anticoagulants/antiplatelet agents be made after careful assessment of the risks of discontinuation (thrombosis risk) and continuation (bleeding risk). It is recommended that this be a shared decision-making process with the patient’s treating physician(s).
References


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