Regional anaesthesia and antithrombotic drugs

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Key points
Vertebral canal haematoma is a rare but potentially devastating complication of central neuraxial blockade. Significant risk factors include clotting abnormalities and drug-induced coagulation disturbance. Careful timing of administration of antithrombotic drugs in relation to regional anaesthesia is important to minimize potential bleeding complications. Several new classes of antithrombotic drugs have been introduced into clinical practice over recent years. These are often used in combination making risk assessment difficult. Local policies should be developed to allow predictable time intervals between administration of antithrombotic drugs and performance of regional anaesthesia.

The benefits of regional anaesthesia are well documented. However, with an increasing number of patients receiving antithrombotic medication, concerns exist about the risk of perineural bleeding complications or neurological damage from compressive vertebral canal haematoma (VCH). Patients taking antithrombotic agents often stand to gain the most benefit from regional anaesthesia, but establishing the balance between risk and benefit can be difficult.

VCH is a very rare but potentially devastating complication of central neuraxial blockade (CNB). Without rapid diagnosis and surgical decompression, permanent neurological damage is likely. Risk factors associated with VCH occurring after CNB were identified by Vandermeulen’s review of case reports from 1906 to 1994.1 Of these 61 cases, 68% occurred in patients either taking anticoagulant drugs (25 received heparin) or those with a coagulopathy. An epidural technique was used in 75 patients, and 66% had an epidural catheter sited. In half of these patients, bleeding occurred immediately after catheter removal, demonstrating that this procedure is as important as catheter insertion. The other major risk factor was technical difficulty with the block. The Royal College of Anaesthetists national audit of major complications of CNB estimated that over 700 000 central neuraxial blocks are performed annually in the UK. Eight cases of VCH were reported over the year (six meeting audit inclusion criteria) all occurring after elective surgery in patients with an epidural catheter for postoperative pain management. Seven of these patients had received an antithrombotic drug either at the time of epidural catheter insertion or removal (warfarin, aspirin, and/or low-molecular-weight heparin (LMWH)). Increasing age, female sex, and significant co-morbidities also appeared to be risk factors. The estimate of the incidence of permanent harm from VCH was reported to be ~1 in 20 000 for perioperative epidurals and 1 in 140 000 for all CNB.

Over recent years, several new classes of antithrombotic agents have been introduced into clinical practice. These drugs are often used in combination, making risk assessment difficult. A number of countries have developed clinical guidelines to recommended ‘safe’ time intervals between drug administration and performing CNB.2–4 These are based on pharmacokinetics, expert opinion, and case reports. For certain anticoagulants, it has been suggested that CNB or removal of a neuraxial catheter should be delayed until at least two half-lives have passed, after which only 25% of the drug remains active.5 A balance between the benefits (prevention of thrombosis) and risks (major bleeding and VCH) should be determined for each patient and depends on the type and dose of antithrombotic, the choice of a regional technique, and patient characteristics. This article will discuss antithrombotic agents in the current UK practice and timing of administration in relation to regional anaesthesia.

Antiplatelet agents
Aspirin and non-steroidal anti-inflammatory drugs

These drugs impair platelet function by inhibiting platelet cyclo-oxygenase (COX). Aspirin inhibits COX irreversibly, whereas non-steroidal anti-inflammatory drugs (NSAIDs) do so reversibly. The antiplatelet effect of aspirin persists until a new platelet population is manufactured (~7 days), whereas platelet function generally returns to normal within 2–3 days after stopping an NSAID. The normal aspirin dose for antiplatelet activity is 75 mg daily. When given in isolation, NSAIDs including aspirin do not increase the risk of VCH and are not a contraindication to CNB. This view is currently endorsed by a number of national
guidelines. When NSAIDs, including aspirin, are used in combination with other drugs that affect coagulation, an increased risk of bleeding complications exists. The current guidance from the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommends against using CNB in patients receiving NSAIDs when the concurrent use of other medication affecting coagulation, for example, LMWH, is planned in the early postoperative period. The European Society of Anaesthesiology suggests commencing thromboprophylaxis after operation rather than before operation in the presence of aspirin.

Thienopyridines

Clopidogrel (half life of 6–8 h) and prasugrel (half life around 7 h) are potent antiplatelet agents. They reduce platelet aggregation by the irreversible inhibition of the platelet P2Y12 ADP receptor and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa (GPIIb/IIIa) complex. Platelets are affected for the remainder of their life span with recovery of platelet function taking at least 7 days. The normal maintenance dose of clopidogrel is 75 mg daily and prasugrel is 10 mg (5 mg if <60 kg or >75 yr old). Prasugrel is currently licensed for use with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). It exerts its antiplatelet effect more consistently and to a greater extent than clopidogrel but is associated with an increased risk of major bleeding. There are many studies in the cardiothoracic literature relating clopidogrel use to an increased risk of postoperative bleeding and transfusion requirements, but little published with regards to general surgery. A recent study of clopidogrel use in patients undergoing non-elective orthopaedic surgery demonstrated no increase in blood loss or transfusion requirements compared with patients not taking clopidogrel. All the patients in the clopidogrel group received a general anaesthetic.

The actual risk of VCH with the thienopyridines is unknown. There are no reported cases of VCH associated with prasugrel to date. Clopidogrel therapy has been implicated in ‘spontaneous’ VCH demonstrating the potency of these drugs; however, there are only a few published case reports associated with CNB. Co-administration of LMWH was an additional risk factor in two of these reported cases. Lumbar epidural catheter placement in 306 vascular surgical patients in whom clopidogrel treatment was continued perioperatively reported no postoperative neurological complications. The study sample size was small, and consequently, CNB in this situation is not endorsed by the authors, recommending larger prospective studies in order to provide more accurate recommendations. The product data sheets for both clopidogrel and prasugrel currently recommend discontinuing at least 7 days before surgery and this interval should be observed before performing CNB. The current published guidelines support this time interval. A period of 7–10 days has been recommended for prasugrel due to the higher incidence of bleeding when compared with clopidogrel.

Dual antiplatelet therapy (DAPT) is well established in the management of ACS, PCI, and coronary stent insertion. Prematurely discontinuing or withholding antiplatelet agents for even a brief period risks stent thrombosis. In one study, more than 25% of patients who discontinued clopidogrel within the first month after drug-eluting stent (DES) placement suffered stent thrombosis. A minimum of 6 weeks DAPT after bare-metal stent insertion and at least 12 months after DES placement is recommended to avoid thrombotic complications. If surgery cannot be delayed beyond these high-risk periods, consultation with a cardiologist is strongly recommended before any planned intervention of treatment and an individual management plan formed. Heparin therapy alone has no antiplatelet properties and is unlikely to protect against stent thrombosis. Replacement with a short-acting reversible antiplatelet agent, for example, a tirofiban infusion, has been suggested, although the evidence is limited and it is currently an unlicensed indication. In an emergency situation, a multidisciplinary approach is also required to explore the potential risks and benefits to the patient.

Dipyridamole

Dipyridamole has antiplatelet and vasodilating actions and is often used in combination with aspirin in the management of cerebrovascular disease. The half life is ~10 h. There are a lack of data in the literature with regard to regional anaesthesia and dipyridamole. The current guidelines suggest that when used alone, there is no need to discontinue before CNB.

GPIIb/IIIa receptor antagonists

Abciximab, eptifibatide, and tirofiban are primarily used in the management of ACS and PCI. Abciximab is a monoclonal antibody and although low levels of GPIIb/IIIa receptor blockade are present for more than 10 days after cessation of abciximab infusion, platelet function typically returned to normal over a period of 24–48 h. Platelet function returns to baseline 6–8 h after discontinuing eptifibatide and tirofiban. CNB should be avoided until these time periods have elapsed and platelet function has recovered. These drugs should be used with caution if required in the postoperative period after CNB, and the patient monitored neurologically. Epidural catheters should be removed before starting these drugs.

Parenteral anticoagulants

Unfractionated heparin

Unfractionated heparin (UFH) has been used for many years for thromboprophylaxis, therapeutic anticoagulation, and the priming of extracorporeal circuits. I.V. heparin provides an immediate anticoagulant effect which lasts for 4–6 h. It can be monitored with the activated partial thromboplastin time (APTT) and one of its advantages is the availability of protamine for rapid reversal.
Administration of subcutaneous UFH for thromboprophylaxis does not usually prolong the APTT; however, with prolonged administration (>4 days), the platelet count should be checked before a regional technique or catheter removal due to the incidence of heparin-induced thrombocytopenia (HIT). The incidence of HIT is ~3% in postoperative patients receiving UFH compared with 0.1–1% in patients on LMWH. Full therapeutic anticoagulation with heparin is a contraindication to regional block. I.V. heparin infusion should be discontinued for 2–4 h and the APTT normal before regional block or catheter removal.

Intraoperative heparin administration in combination with neuraxial blockade does not appear to present a significant risk. Most published case series used similar guidelines for patient management; exclusion of high-risk patients (pre-existing coagulopathy) and performance of CNB at least 1 h before heparin administration. Although the occurrence of a bloody tap or difficult needle placement when intraoperative heparinization is planned intuitively increases the risk, there are no data to support compulsory cancellation of surgery. Some suggest avoiding low-dose anticoagulation (5000 IU heparin) for 1–2 h and full intraoperative heparinization for 6–12 h. Communication with the surgeon and a risk–benefit decision about proceeding for each case would be a reasonable approach.

Epidural anaesthesia and heparinization for cardiopulmonary bypass remains controversial. Case reports of VCH after high thoracic epidural anaesthesia in cardiac surgery have been published, but are rare. The accepted benefits need to be carefully weighed against the potentially catastrophic outcome of a high thoracic VCH.

Low-molecular-weight heparin
LMWHs potentiate factor Xa inhibition and are used for thromboprophylaxis, treatment of venous thromboembolism (VTE), and in unstable coronary artery disease. Compared with UFH, LMWHs have a longer half-life (prolonged in renal impairment), more predictable pharmacokinetics, and less effect on platelet function. They are not reliably reversed by protamine sulphate and anti-Xa activity is not measured by routine laboratory assays. LMWHs have a similar clinical efficacy and a comparable risk of VCH.

After the introduction of enoxaparin in the USA in 1993, more than 50 VCHs were reported. This cluster of cases had not occurred in Europe, despite millions of patients receiving LMWH and CNB. Analysis of these patients estimated the risk of VCH to be 1 in 40,000 after spinal anaesthesia and 1 in 3000 after epidural anaesthesia, the majority occurring at the time of catheter removal in elderly orthopaedic patients. The different dosing strategy used in the USA was one possible explanation; 30 mg twice daily compared with 20 or 40 mg once daily in Europe.

The current guidelines recommend waiting 12 h after the last prophylactic dose of LMWH before CNB or epidural catheter removal. Administration the evening before surgery, or after operation, is therefore appropriate. After CNB or catheter removal, a period of 2–4 h should elapse before LMWH administration.

When LMWHs are administered in therapeutic doses for anticoagulation (typical doses; enoxaparin 40–100 mg twice daily, dalteparin 5000–10,000 units twice daily, depending on body weight), an interval of at least 24 h should elapse before regional anaesthesia. There are no clear guidelines with regard to the accumulation of LMWH in renal impairment and subsequent time intervals for attempting a regional technique. The risks and benefits will require consideration in each individual case and extra vigilance after operation if a regional technique is used.

Fondaparinux
Fondaparinux is a synthetic pentasaccharide that has potent anticoagulant activity. It selectively inhibits factor Xa, does not inactivate thrombin, and has no effect on platelets. It is licensed for use in thromboprophylaxis in medical patients and in patients undergoing major lower limb orthopaedic surgery or abdominal surgery. After a single subcutaneous injection, peak plasma concentration occurs after 2 h. The half-life is 17–21 h in healthy patients, but this may be significantly prolonged in renal impairment.

The risk of VCH with fondaparinux is as yet unknown and the current guidelines are based on the prolonged half-life. For VTE prophylaxis, 2.5 mg is administered once daily and it is started 6 h after operation, provided surgical haemostasis is established (manufacturer’s recommendation). This makes decisions with respect to regional anaesthesia easier. When continuous catheter techniques are planned, however, the prolonged half-life makes the decision less straightforward. The EXPERT study demonstrated that neuraxial or deep peripheral nerve catheters can be used safely in patients receiving once-daily prophylactic dose fondaparinux, provided a drug-free period of 48 h is observed; 36 h before catheter removal and re-starting treatment 12 h after catheter removal. No neuraxial or perineural haematomas occurred, and although no increase in VTE risk was demonstrated, this regime does result in a significant time period without VTE prophylaxis. This study lacked sufficient power to reach any firm conclusions, and the current guidance recommends against the use of indwelling neuraxial catheters with fondaparinux.

CNB is not recommended when fondaparinux is used for therapeutic anticoagulation.

Oral anticoagulants
Warfarin
Approximately 1% of the UK population are currently taking warfarin; the most common indication being atrial fibrillation. Warfarin inhibits the synthesis of the vitamin K-dependent clotting factors (II, VII, IX, and X) and is indicated for VTE prophylaxis in a number of conditions. Therapeutic anticoagulation with warfarin is an absolute contraindication to CNB. For all but the most minor procedures, warfarin should be discontinued 4–5 days before surgery allowing the international normalized ratio (INR) to
decrease to ≤1.5. This value is associated with clotting factor activity levels >40% and essentially normal haemostasis. Warfarin should only be recommenced once an epidural/nerve catheter has been removed. In emergency situations, warfarin can be reversed with vitamin K, prothrombin complex concentrates, or fresh frozen plasma.

### Oral thrombin blockers

Dabigatran and rivaroxaban have recently been introduced into clinical practice and are currently licensed for thromboprophylaxis after elective hip and knee arthroplasty. Owing to their predictable pharmacokinetics and pharmacodynamics, they do not require monitoring and are convenient for extending VTE prophylaxis after hospital discharge. Unfortunately, there is currently no way of reversing the antithrombotic effects of these drugs and it will take up to 24 h until coagulation returns to normal. This will have implications for patients who need urgent surgery and anaesthesia and are on these drugs.

### Dabigatran

Dabigatran is a potent direct oral thrombin inhibitor. Recommended dose for VTE prophylaxis is 110 mg 1–4 h after surgery followed by 220 mg daily (150 mg if ≥75 yr). It has a rapid onset of action with peak plasma concentrations occurring within 2–4 h. The half-life ranges from 14 to 17 h. The British National Formulary states that it can be commenced 1–4 h after surgery and is recommended for 10 days after knee replacement and 28–35 days after hip replacement. A reduced dose is advised in renal impairment, and plasma concentrations can be elevated when co-administered with verapamil, amiodarone, and clarithromycin. The manufacturer recommends a minimum time period of 2 h after epidural catheter removal before starting dabigatran after operation; however, the current guidelines suggest 6 h based on the initial studies in which all epidural catheters were removed at least 4–6 h before the first dose.

### Rivaroxaban

Rivaroxaban is a direct inhibitor of factor Xa. It does not inhibit thrombin and has no effect on platelets. It is rapidly absorbed with peak plasma concentrations occurring after 2–4 h. The half-life ranges from 7 to 11 h. Elderly patients exhibit higher plasma concentrations due to reduced total and renal clearance; however, no dose adjustment is necessary. It is currently licensed for VTE prophylaxis after primary hip and knee replacement in the UK. It is likely that it will be licensed for prophylaxis in atrial fibrillation patients in the near future. The initial dose (10 mg) is administered

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**Table 1 Suggested guideline for the management of warfarinized patients for elective procedures (adapted from the NHS Tayside guideline)**

- Procedures with a low bleeding risk or where the potential site of bleeding is easily accessible may be performed without warfarin reversal if the INR is within the target range
- For surgery, more invasive procedures aim for INR ≤1.5

**Low-risk patients (most patients)**

- Atrial fibrillation or valvular heart disease, not complicated by a previous arterial thrombotic event
- Venous thromboembolism >3 months ago

**Plan**

- Stop warfarin for 5 days
- Check INR the day before surgery
  - INR ≤1.5—proceed
  - INR 1.6–1.7—give 1 mg oral vitamin K
  - INR ≥1.8—give 2 mg oral vitamin K

- Repeat INR on day of procedure to ensure ≤1.5
- After operation (if no excess bleeding)
  - Restart warfarin on the day of procedure at patient’s normal maintenance dose
  - Give standard VTE heparin prophylaxis until the INR is within range
  - Measure INR at 48 h

**High-risk patients**

- Atrial fibrillation or valvular heart disease complicated by an arterial thrombotic event
- Venous thromboembolism <3 months ago
- Mechanical non-bioprosthetic heart valve/multiple heart valve replacements
- Patients with target INR of 3.0–4.5
- Patients not clearly in the low-risk groups

**Plan**

- Discuss heparin bridging therapy (at therapeutic doses) while the INR is outside the target range with haematology/vascular medicine/cardiology and agree the dose to be used for each individual patient
- Stop warfarin as above
- Bridging therapy is usually commenced on the third morning after the last evening dose of warfarin
- Stop to allow clearance pre-surgery (2–4 h for unfractionated heparin and 24 h for LMWH)
- Restart heparin bridging after operation and recommence warfarin at usual maintenance dose

6–10 h after surgery and recommended for 35 days after hip replacement and 14 days after knee replacement. The current guidelines and the manufacturer recommend a 12–18 h period between dosing and epidural catheter removal, and the next dose to be delayed for at least 6 h to reduce the risk of VCH. The manufacturer also recommends delaying dosing for 24 h after a traumatic puncture. There is limited experience and evidence with these newer agents, and caution should be exercised when combining these with neuraxial techniques.

### Peripheral nerve block

The complications of peripheral nerve blocks are generally less serious than those of CNB, although significant and even fatal retroperitoneal haematomas have been reported after lumbar sympathetic blockade in patients on thienopyridines (clopidogrel and
ticlopidine). To apply the same guidelines used for CNB to all peripheral nerve blocks is unnecessarily restrictive. Differentiation between deep (e.g. lumbar plexus) and superficial (e.g. axillary, femoral) nerve blocks may be more appropriate. The Austrian Society of Anaesthetists advise stopping VTE prophylaxis and antplatelets before deep peripheral nerve blocks where access is difficult and arterial trauma a risk, for example, interscalene, supravacular, infravacular, and lumbar sympathetic blocks. Where possible, the same time intervals recommended between anticoagulant administration and CNB should be followed for peripheral nerve catheter insertion or withdrawal.

**Heparin bridging therapy: when is it necessary?**

Approximately 1% of the UK population are on lifelong warfarin, the most common indication being atrial fibrillation. The risks of thrombosis vs bleeding need to be quantified before a decision can be made about perioperative drug management. Even temporary interruption of these drugs may increase the risk of thrombosis with potential for morbidity and mortality. The risk is greatest in patients with previous arterial thrombotic events. The risk depends on the indication for anticoagulation and the absolute risk that an individual will have a thrombotic event. For example, without anticoagulation, the highest risk for recurrent thrombosis is within the first 3 months after extracapsular cataract removal and cystoscopy, may not require interruption of anticoagulation; however, this is usually required for major surgery. In patients with a high risk of thromboembolism (Table 1), bridging therapy is recommended. Estimated rates of thromboembolism without anticoagulation for various indications are available in the literature. Risk stratification of patients is often not straightforward and requires a multidisciplinary approach with the development of local policies. Local policies should also be developed to allow predictable dosing of LMWH and hence predictable time intervals between administration and performance of regional anaesthesia (Table 2). The majority of patients who are taking lifelong warfarin fall into the low-risk group and do not need perioperative heparin bridging.

**Table 2** Suggested time intervals for antithrombotic administration before and after CNB/catheter removal (adapted from SIGN and the European Society of Anaesthesiology guidelines)²,⁴

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time interval to discontinue before CNB or catheter removal</th>
<th>Time interval to (re)commence after CNB or catheter removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and NSAIDs</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 days</td>
<td>After catheter removal</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7–10 days</td>
<td>6 h after catheter removal</td>
</tr>
<tr>
<td>Unfractionated heparin prophylaxis (subcutaneous)</td>
<td>4–6 h</td>
<td>&gt;1 h</td>
</tr>
<tr>
<td>Unfractionated heparin treatment (i.v.)</td>
<td>Stop infusion 2–4 h before (check APTT)</td>
<td>2–4 h</td>
</tr>
<tr>
<td>LMWH (prophylactic dose)</td>
<td>12 h</td>
<td>2–4 h</td>
</tr>
<tr>
<td>LMWH (therapeutic dose)</td>
<td>24 h</td>
<td>6 h after surgery/CNB</td>
</tr>
<tr>
<td>Fondaparinux (for prophylaxis)</td>
<td>36 h</td>
<td>12 h after catheter removal</td>
</tr>
<tr>
<td>Warfarin</td>
<td>INR ≤1.5</td>
<td>After catheter removal</td>
</tr>
<tr>
<td>Dabigatran (started postop.)</td>
<td>Use is contraindicated by the manufacturer with postop. indwelling epidural catheters</td>
<td>6 h</td>
</tr>
<tr>
<td>Rivaroxaban (started postop.)</td>
<td>12–18 h</td>
<td>6 h</td>
</tr>
</tbody>
</table>

with thrombosis (n=4), although no deaths were associated with either complication. Minor surgical procedures, for example, extracapsular cataract removal and cystoscopy, may not require interruption of anticoagulation; however, this is usually required for major surgery. In patients with a high risk of thromboembolism (Table 1), bridging therapy is recommended. Estimated rates of thromboembolism without anticoagulation for various indications are available in the literature. Risk stratification of patients is often not straightforward and requires a multidisciplinary approach with the development of local policies. Local policies should also be developed to allow predictable dosing of LMWH and hence predictable time intervals between administration and performance of regional anaesthesia (Table 2). The majority of patients who are taking lifelong warfarin fall into the low-risk group and do not need perioperative heparin bridging.

**Declaration of interest**

None declared.

**References**


Please see multiple choice questions 9–12.