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Central neural blockade in patients with a drug-induced alteration of coagulation
Third edition of the Belgian Association for Regional Anaesthesia (BARA) Guidelines

Approved by the boards of the Belgian Professional Association of Specialists in Anesthesia and Resuscitation and the Society of Anesthesia and Resuscitation of Belgium (SBAR)
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The first edition of the Belgian guidelines on antithrombotics and central neuraxial anesthesia was published in the year 2000, followed by the second edition in 2005 (1, 2). These guidelines provided Belgian anesthetists with a framework to hold on to when managing patients treated with antithrombotic therapy. Since 2005, however, new information on the risk of central neural blocks in patients treated with antithrombotics has emerged and new antithrombotic agents have become available. In our modern Western civilization, cardiovascular disease remains the number one cause of morbidity and mortality and – as our population ages progressively – there is an increased need for drugs that prevent or treat arterial and/or venous thromboembolism. In addition, case reports suggesting that the risk of a spinal hematoma may be higher than previously thought (3-7) continue to appear in the anesthetic literature. Taken together, these facts all substantiate the necessity of an update of these guidelines.

Guidelines

There are virtually no prospective data on the use of central neuraxial anesthetic techniques in the presence of antithrombotic drugs. The majority of the available recommendations and guidelines on the subject are expert opinions based on large case series, case reports and the pharmacological data of the individual antithrombotic drug involved. The resulting recommendations will always include : (1) a minimum time interval that should be observed between the last dose of an antithrombotic drug and the insertion of a neuraxial needle/catheter or the manipulation/removal of that catheter, (2) a minimum time interval that should be observed between the insertion of a neuraxial needle/catheter or the manipulation/removal of that catheter and the next dose of antithrombotic, and in some cases, (3) the need to perform a coagulation test prior to the performance of a neuraxial anesthetic technique.

For most of the antithrombotics included in the present guidelines, there is a large body of knowledge and experience available as they have been available for some time. However, when new drugs are discussed, it becomes more complicated. New antithrombotic agents may differ in the onset of action, the half-life and the antithrombotic potency. Unfortunately, more potent antithrombotic efficacy goes hand in hand with increased bleeding risk, whereas antagonizing agents are currently not available for the new antithrombotics. Because of the lack of experience with these new drugs, it is mainly the pharmacological profile that must guide

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Table 1

Classes of recommendation and levels of evidence

Classes of recommendations	
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial
Class II	Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa	Weight of evidence/opinion in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful
Level of evidence	
Level A	Data derived from multiple randomised clinical trials or meta-analyses
Level B	Data derived from a single randomised clinical trial or large non-randomised studies
Level C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries

the clinician when using central neuraxial anesthesia in patients treated with these new drugs. ROSENCHER *et al.* proposed a strategy that can be applied when new antithrombotic agents are used for prophylaxis of venous thromboembolism (8). In the presence of these drugs, central neuraxial insertion of a needle and/or catheter and the subsequent manipulation/withdrawal of the catheter should only be performed at least 2 elimination half-lives after the last dose of an antithrombotic has been administered. Subsequently, the first or next dose of that antithrombotic should only be administered after a time interval obtained by subtracting the time necessary for that specific antithrombotic to reach therapeutic plasma levels after administration, from the time necessary to produce a stable blood clot (i.e. 8 h).

The grading of the recommendations and the level of evidence of the present guidelines has been obtained by using the definitions of the Committee for Practice Guidelines of the European Society of Cardiology (ESC) (Table 1) (9). Also, these guidelines are not intended to bypass the clinical judgment of the anesthetist. However, when the anesthetist decides not to comply with these guidelines, we recommend to document the rationale in the patient's chart and informed consent from the patient should be obtained.

Preferably, the perioperative cessation of antithrombotic drugs so as to safely perform a regional block should be discussed with the physician who initiated this therapy and the surgeon. An alternative anesthetic technique should be used if it is judged that the administration of the antithrombotic must not be interrupted, e.g. in patients with recent coronary stenting.

The time windows mentioned in the present guidelines are only valid in patients with a normal pharmacological profile (Table 2). This includes a normal body weight, and normal hepatic and renal function.

The simultaneous administration of different antithrombotic drugs is not considered. Such combinations may increase the risk of perioperative hemorrhagic complications and necessitate greater caution.

The antithrombotic agents that will be discussed in detail hereafter are : low molecular weight heparins (LMWHs), unfractionated heparin (UH), selective factor Xa inhibitors, direct thrombin inhibitors, vitamin K antagonists (VKAs), non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents and fibrinolytic/thrombolytic agents. A list of these drugs with both their generic and registered trade names is included in the text (Table 3). Danaparoid, argatroban and cilostazol are not (routinely) available in Belgium and are thus not addressed in this text. If necessary, recommendations concerning these drugs and neuraxial anesthesia can be found in the recently published European Society of Anaesthesiology (ESA) recommendations (10). Finally, a small section addressing the issue of herbal medicines is included at the end.

RISK OF SPINAL HEMATOMA

Spinal hematomas are rare and mainly occur spontaneously (11). In most cases, no direct cause or contributing factor can be identified. Still, the second and third most commonly identified causes are concurrent antithrombotic therapy and the

Table 2

Summary of recommended minimum time intervals or clotting times before and after central neuraxial needle puncture/catheter insertion, manipulation or removal of catheters*

Antithrombotic agent	Before puncture/catheter insertion/manipulation or removal	After puncture/catheter insertion/manipulation or removal	Laboratory investigations
LMWH (prophylactic dose)#	12 h	4 h	Platelet count if LMWH > 5 d
LMWH (intermediate or therapeutic dose)£	24 h	4 h	Platelet count if LMWH > 5 d
UH (therapeutic dose)	aPTT and/or ACT within normal range	1 h	aPTT, ACTPlatelet count if UH > 5 d
Fondaparinux	36-42 h	6-12 h	Anti-Xa activity – assay standardized for specific agent§
Rivaroxaban (≤ 10 mg/d)	22-26 h	6 h	Anti-Xa activity – assay standardized for specific agent§
Rivaroxaban (>10 mg/d)	3 d	6 h	Anti-Xa activity – assay standardized for specific agent§
Apixaban (≤ 2.5 mg bid)	26-30 h	6 h	Anti-Xa activity – assay standardized for specific agent§
Apixaban (> 2.5 mg bid)	3 d	6 h	Anti-Xa activity – assay standardized for specific agent§
Lepirudin	8-10 h	2-4 h	aPTT, ECT
Dabigatran (≤ 220 mg/d)	Contraindicated according to manufacturer	6 h	TT, ECT
Dabigatran (> 220 mg/d)	4 d	6 h	TT, ECT
Vitamin K antagonists	INR ≤ 1.4	After catheter removal	INR
NSAIDs	None	None	
Dipyridamole	None	None	
Acetylsalicylic acid	None	None	
Ticlopidin	10 d	After catheter removal	
Clopidogrel	7 d	After catheter removal	
Prasugrel	10 d	6 h	
Ticagrelor	7 d	6 h	
Eptifibatide / tirofiban	8-10 h	2-4 h	Platelet count
Abciximab	48 h	2-4 h	Platelet count

ACT, Activated clotting time ; aPTT, activated partial thromboplastin time ; ECT, ecarin clotting time ; INR, international normalised ratio ; NSAIDs, non-steroidal anti-inflammatory drugs ; TT, thrombin time. *All time intervals apply to patients with normal body weight and normal hepatic/renal function. #Maximum prophylactic dosages of low molecular weight heparins are listed in Table 4. £ Intermediate and therapeutic doses of LMWH are listed in Table 4. § Under development.

presence of vascular malformations. In contrast, for spinal bleeding associated with neuraxial anesthesia, the use of antithrombotic therapy is the most important risk factor (12, 13). Because of the rarity of this dramatic event, it is virtually impossible to get an accurate estimate of its incidence through prospective studies. Estimates are often based on the analysis of case reports. In 1993, Tryba estimated the incidence of a spinal hematoma to be 1 in 150 000 and 1 in 220 000 patients after epidural or spinal anesthesia, respectively (14). More recent data suggest that the actual incidence might be higher, in particular in association with the use of antithrombotic agents. Incidences ranging from 1 in 1000 to 1 in 10 000 neuraxial blockades were reported in orthopedic patients treated with enoxaparin (15). The presence of an impaired coagulation increased the bleeding incidence to 1 in 40 800, 1 in

Table 3

Generic and registered trade names of antithrombotic agents currently available in Belgium

	Generic name	Registered trade name
Low molecular weight heparin	Enoxaparin Dalteparin Nadroparin Tinzaparin	Clexane® Fragmin® Fraxiparine® Fraxodi® Innohep®
Unfractionated heparin	Heparin	Heparine Leo® Heparine Natrium B. Braun®
Selective factor X inhibitors	Fondaparinux Rivaroxaban Apixaban*	Arixtra® Xarelto® Eliquis®
Direct thrombin inhibitors	Lepirudin Dabigatran	Refludan® Pradaxa®
Vitamin K antagonists	Acenocoumarol Phenprocoumon Warfarin	Sintrom® Marcoumar® Marevan®
Acetylsalicylic acid	Acetylsalicylic acid	Acenterine® Alka Seltzer® Asaflow® Asa Mylan® Asa Sandoz® Aspegic® Aspirine® Cardegic® Cardioaspirine® Cardiphar® Dispril® Sedergine® Tampyrine®
Dipyridamol	Dipyridamol	Dipryridamole EG® Persantine®
Acetylsalicylic acid + Dipyridamol	Acetylsalicylic acid + Dipyridamol	Aggrenox®
Thienopyridines	Clopidogrel Prasugrel Ticlopidin	Clopidogrel Apotex® Clopidogrel Doc® Clopidogrel EG® Clopidogrel Mylan® Clopidogrel Sandoz® Clopidogrel Teva® Plavix® Efient® Ticlid® Ticlopidine EG® Ticlopidine Teva® Ticlopidin Ratiopharm®
Pyrimidines	Ticagrelor*	Brilique®
Glycoprotein IIb/IIIa receptor antagonists	Abciximab Eptifibatide Tirofiban	Reopro® Integrilin® Aggrastat®
Fibrinolytic/thrombolytic agents	Alteplase Tenecteplase Reteplase Urokinase	Actilyse® Metalyse® Rapilysin® Actosolv®

* Not registered in Belgium yet.

6600 and 1 in 3100 patients following spinal anesthesia, single-shot epidural anesthesia and epidural catheter techniques, respectively (7). Even more worrisome were the findings of a Scandinavian survey that was published in 2004 (6). The authors reported a spinal hematoma in 1 in 3600 female patients undergoing knee arthroplasty under epidural anesthesia. More recent case series confirm these higher incidences (3, 4, 16), although somewhat more reassuring figures were published by Cook *et al*., who found and incidence of vertebral canal hematoma ranging from 1 in 88 000 to 1 in 140 000 central neuraxial blocks (5). This study furthermore reported that the pediatric and obstetric populations have the lowest risk in terms of spinal bleeding, which thereby confirms previous reports that the incidence of spinal hematoma after neuraxial blocks is lowest in the obstetric population with incidences ranging from 1 in 168 000 to 1 in 200 000 women (6, 17).

General recommendations

Contributing factors

Routine laboratory investigations do not always detect a hemorrhagic diathesis. A thorough patient history and clinical examination are mandatory to detect an increased bleeding tendency. Several conditions may be associated with altered coagulation, such as the perioperative use of various antithrombotic drugs, a low platelet count, renal and/or hepatic failure, chronic alcoholism, chronic steroid therapy, and the perioperative infusion of dextrans. Unfractionated heparin and LMWHs alone or in association with acetylsalicylic acid (ASA), NSAIDs and/or thienopyridines are the drugs most commonly involved (18). Other risk factors include bloody, traumatic and/or multiple punctures, the use of large bore needles, anatomic abnormalities of the spinal cord, vascular malformations in the vicinity of the spinal cord (12, 19), osteoporosis with spinal stenosis (6), Bechterew's disease (20), preexisting spinal canal pathology (21), the lack of guidelines on the use of central neuraxial techniques in the presence of antithrombotics (6), female sex (6, 16, 22) and advanced age (5, 6, 16). Advanced age is associated with degenerative spine disorders and renal insufficiency. As the elimination of many antithrombotic drugs is kidney dependent, renal insufficiency may prolong and intensify the anticoagulant effects, thereby increasing the bleeding risk if no dose adjustment is performed. Finally, the use of epidural catheters, and particularly their removal, is associated with the highest bleeding risk, as almost two thirds of the hematomas were described only after withdrawal of the catheters (5, 6, 12, 18). If neuraxial blockade is considered beneficial to a given patient, a spinal anesthetic technique may be a valuable alternative since current data from the literature suggest that spinal puncture may be associated with a lower risk of spinal hematoma when compared to epidural or combined spinal-epidural anesthetic techniques (5, 7) (Class IIa, level C).

Spinal hematoma

All patients should be carefully observed for signs of a developing spinal hematoma after neuraxial blockade or after removal of the neuraxial catheter. A slow or absent regression of motor and/or sensory block, back pain, urinary retention, and the return of a sensory and motor deficit after a previous (complete) regression of the block, alone or in combination, suggest a developing spinal hematoma (Class I, level B). Patients, nurses and physicians should be taught the signs of a spinal hematoma and should be instructed to contact an anesthetist immediately (Class IIa, level C). Postoperative analgesia with low concentrations and/or low doses of local anesthetics and the insertion of the epidural catheter at the thoracic level will produce a minimal or absent motor block of the lower limbs and thus facilitate the early detection of a developing hematoma. In case of any doubt, the epidural infusion of local anesthetics should be stopped immediately in order to detect any neurological deficit as soon as possible.

When a clinical suspicion of spinal hematoma formation arises, an aggressive diagnostic and therapeutic approach is mandatory (Class I, level C). This includes urgent magnetic resonance imaging (MRI) or a CT scan. If the diagnosis is confirmed, a decompressive laminectomy should be performed less than 8 to 12 h after the appearance of the first symptoms of medullary compression in order to keep the patient's chances of making a complete neurological recovery intact (Class I, level B) (12, 23).

It is advisable that written protocols for the management of suspected spinal hematoma, covering the assessment of motor and sensory function, the diagnostic work-up with MRI or CT scanning, and the referral to neurosurgery, are available in every institution (10, 24) (Class IIb, level C).

Thromboprophylaxis

Currently, LMWHs represent the mainstay of perioperative thromboprophylaxis. There are only small differences in efficacy between a pre- or postoperative start. Both options are acceptable (25-27), and in line with the most recent guidelines from the American College of Chest Physicians (ACCP) (28). However, as antithrombotic drugs increase the risk of spinal bleeding after neuraxial anesthetic techniques, we recommend to start prophylactic LMWHs only postoperatively, especially in patients also treated with ASA (Class IIb, level B).

Regional anesthesia itself has some protective effects against the occurrence of thromboembolic complications. Improved pain relief allows an earlier mobilisation of the patients. Although the inhibition of a surgical stress reaction and local anesthetics alter coagulation and fibrinolysis (29, 30), regional anesthesia by itself does not increase bleeding tendency (31) or has a thromboprophylactic activity equivalent to or exceeding that of current thromboprophylactic compounds (32).

Low molecular weight heparins

Prophylactic administration

Low molecular weight heparins are fragments of UH that cause an antithrombin dependent inhibition of factors IIa and Xa. Bioavailability is almost 100% and the half-life is approximately of 4 to 7 h. A once-daily dosing has been well validated for thromboprophylaxis. Prophylactic regimens of the different LWMHs currently available are mentioned in Table 4.

Since the appearance of the first guidelines in 2000, the attitude towards patients receiving prophylactic doses of LMWHs has not changed. An interval of at least 12 h between the last prophylactic dose of LMWH and the subsequent neuraxial blockade should be respected (Class IIa, level C). When prophylaxis is initiated after the procedure, the administration of LMWHs should be delayed until 4 h after the neuraxial technique (Class IIa, level C).

A neuraxial catheter should not be manipulated or removed earlier than 12 h after LMWH administration (Class IIa, level C). The subsequent dose of a LMWH should be delayed until at least 4 hours after the removal of manipulation of the neuraxial catheter (Class IIa, level C). LMWHs can induce thrombocytopenia (i.e. heparin-induced thrombocytopenia or HIT), although the incidence is 10 times lower than for UH (33). A platelet count in patients that are or have been on LMWHs for at least 5 d is advised (Class I, level B) (34).

Therapeutic administration

Low molecular weight heparins are also used in intermediate (i.e. halftherapeutic) and therapeutic doses in a once or twice daily schedule (Table 4). A neuraxial block should not be performed earlier than 24 h after the last intermediate or therapeutic dose of LMWH (Class IIa, level B). If LMWH treatment is to be continued following the surgical procedure, only prophylactic doses should be used as long as a neuraxial catheter is in place. As discussed previously, a neuraxial catheter should not be removed within 12 h after prophylactic LMWH administration and a time window of at least 4 h before the injection of the subsequent dose needs to be respected (Class IIa, level C). For the first administration of LMWH after neuraxial catheter removal, a prophylactic dose is recommended but therapeutic doses may be used thereafter (Class IIb, level C). Because of the risk of HIT, a platelet count is advised if LMWHs have been used for at least 5 d (Class I, level B) (34).

Unfractionated heparin therapy

Therapeutic preoperative use

Unfractionated heparin produces an anticoagulant effect via an anti-thrombin dependent inhibition of factor IIa and Xa.

An ongoing treatment with therapeutic doses of UH is an absolute contraindication to the performance of a neuraxial anesthetic technique (Class III, level C). However, the cessation of an ongoing UH therapy should always be discussed with the treating physician(s). Before inserting an epidural and/or spinal needle/catheter, the normalization of coagulation parameters must be assessed by laboratory tests such as the activated partial thromboplastin time (aPTT) or the activated clotting time (ACT), which should be within normal limits (Class IIa, level C) (Table 5). The ACT is a point-of-care test (POCT) that can be used as an alternative to the aPTT. The normal values of both the aPTT and ACT will vary from hospital to hospital as they depend upon the specific assay used locally. UH can induce HIT. A platelet count in patients that

Table 4

Prophylactic, intermediate and therapeutic doses of low molecular weight heparins

	Prophylactic doses - SC	Intermediate doses - SC	Therapeutic doses - SC
Clexane® (enoxaparin)	1 × 0,5 mg*/kg/24 h	1 × 20-40 mg*/24 h (1 × 0.5 mg*/kg/24 h)	2 × 1 mg*/kg/24 h or 1 × 1.5 mg*/kg/24 h
Fragmin® (dalteparin)	1 × 2500-5000 IU anti-Xa/24 h	1 × 100 IU anti-Xa/kg/24 h	2 × 100-IU anti-Xa/kg/24 h or 1 × 200 IU anti-Xa/kg/24 h
Fraxiparine® (nadroparin)	1 × 2850-5700 IU anti-Xa/24 h	1 × 90 IU anti-Xa/kg/24 u	2 × 90 IU anti-Xa/kg/24 h
Fraxodi® (nadroparin)	/	/	1 × 171 aXa IU/kg/24 h
Innohep® (tinzaparin)	1 × 50 IU anti-Xa/kg/24 h	1 × 90 IU anti-Xa/kg/24 h	1 × 175 IU anti-Xa/kg/24 h

* 10 mg = 1000 IU anti-Xa (anti-Xa activity).

have been on UH for at least 5 d is advised (Class I, level B) (34).

Therapeutic intraoperative use

The use of UH during surgery does not necessarily preclude the use of a neuraxial anesthetic technique. There is evidence that this can be safely done provided the UH is administered no earlier than at least 1 h after performing the neuraxial anesthetic technique (Class IIa, level C) (35, 36).

In case of a bloody puncture, it is recommended that a low-dose of UH (i.e. 5000 IU) be avoided for 1-2 h and that full intraoperative heparinization is delayed for 6-12 h, and if necessary, to postpone surgery to the next day (Class IIa, level C).

The anesthetist should discuss with the surgeon whether to continue, stop, or temporarily antagonize therapeutic heparin anticoagulation in order to determine the optimal timing for catheter removal.

At all times, catheters should only be removed when the aPTT (Table 5) or the ACT are within normal range (Class IIa, level C) and at least 1 h before any subsequent heparin administration. With the current knowledge, the use of neuraxial techniques remains at the least experimental when higher (i.e. supratherapeutic) doses are used, as is the case in cardiac surgery. Moreover, the use of neuraxial blockade in cardiac surgery does not seem to have any significant effects on morbidity and mortality (37-39), while there is a significant bleeding risk (40). In sum, these findings may question the use of neuraxial techniques in cardiac surgery (Class IIb, level C).

SELECTIVE FACTOR XA INHIBITORS

Fondaparinux

Fondaparinux (Arixtra®) is a synthetic selective inhibitor of factor Xa. With a bioavailability of almost 100 % and an elimination half-life of 18-21 h, plasma levels will still be prophylactic after 24 h. Prophylactic fondaparinux is administered subcutaneously once daily in a dose of 2.5 mg and should be started 6-12 h postoperatively (41). The half-life will be prolonged to 36-42 h if creatinine clearance is 20-50 ml/min, when the dose should be reduced to 1.5 mg (42). Fondaparinux should not be used if creatinine clearance is inferior to 20 ml/min. The preoperative administration of fondaparinux may even increase the risk of intraoperative bleeding without improving its thromboprophylactic efficacy (43). The use of higher doses will increase bleeding tendency and is only approved for therapeutic anticoagulation. Fondaparinux has been successfully used in the treatment of HIT, and the ACCP currently recommends fondaparinux in patients with strongly suspected (or confirmed) HIT as an alternative, non-heparin anticoagulant for thromboprophylaxis (44).

As fondaparinux is started postoperatively, there should be no problem with the preoperative insertion of an epidural/spinal needle for a single-shot anesthetic technique. In case of a bloody tap, an alternative method of thromboprophylaxis should be considered, as insufficient data are available to safely initiate the use of fondaparinux. The long half-life of the drug and its kidney-dependent mode of elimination carry the inherent risk of

Table 5

Laboratory investigations and neuraxial techniques

	Without problems	After individual evaluation
Prothrombin Time (PT)	> 50% (INR* ≤ 1.4)	40-50% (INR* 1.4-1.7)
Activated Partial Thromboplastin Time (aPTT)	Upper limit of normal**	Exceeding upper limit of normal by 1-4 sec**
Platelets	> 80,000/μl	50,000-80,000/μl

* INR, international normalized ratio

** Normal values depend on assay used locally in each hospital.

accumulation, especially in the elderly. This should be taken into account when considering the use of a neuraxial catheter. Moreover, the ACCP currently recommends against the use of continuous epidural analgesia in the presence of fondaparinux (28). Instead, an alternative method of thromboprophylaxis should be used (e.g. LMWH). If for some reason patients with an indwelling epidural/spinal catheter are treated with fondaparinux, the removal of these catheters can be performed under the conditions used in the EXPERT study (Evaluation of arixtra for the prevention of venous thromboembolism in daily practice) (45) : i.e., respecting an interval of 36 h after the last dose of fondaparinux and longer if creatinine clearance is below 50 ml/min, while the next dose of fondaparinux was administered no earlier than 12 h after catheter removal. This practice did not increase the risk of venous thromboembolism, while no spinal epidural hematoma occurred. Still, the statistical power of this study is too low to make any firm recommendations.

If therapeutic doses of fondaparinux (5-10 mg per day) are used, neuraxial anesthesia techniques should not be performed (Class III, level C).

Rivaroxaban and apixaban

Rivaroxaban (Xarelto®) is a selective inhibitor of factor Xa that is administered orally once daily. It is currently approved for the prevention of deep venous thrombosis after total arthroplasty of the knee or the hip. Rivaroxaban is more efficacious than enoxaparin in preventing post-operative venous thromboembolism (46) and first results from the Rocket-AF trial suggest that it may be as effective as warfarin in the prevention of cardioembolism in patients with atrial fibrillation (47). Although initial reports did not show an increased bleeding tendency, a recent document from the U.S. Food and Drug Administration (FDA) warned against the use of rivaroxaban in thromboprophylaxis because of an increased risk for non-major clinical bleeding events when compared to enoxaparin (48). Prophylaxis with rivaroxaban is initiated 6-8 h after surgery and maximum plasma levels will be reached after 2-4 h following the administration of a dose of 10 mg. The drug is eliminated both via the kidney (33%) and the liver and has an elimination half-life of 5-9 h that is therefore only minimally influenced by renal function. According to the manufacturer, the half-life can be prolonged to 11-13 h in the elderly, but a dose adjustment is not necessary. Routine monitoring of the anticoagulant effect is not deemed necessary by the manufacturer although both the prothrombin time (PT) and the International Normalized Ratio (INR) are prolonged in a dose-dependent manner by rivaroxaban. However, neither the PT nor the INR should be used to decide whether or not it is safe to perform a neuraxial block, as these tests were only validated for vitamin K antagonists (VKAs). In the near future, anti-Xa assays validated for the specific agents will become available. As with most new antithrombotics, rivaroxaban cannot be antagonized.

A minimum time interval of 22-26 h should be respected before a neuraxial catheter is removed (Class IIa, level C). The next dose of rivaroxaban should only be given 6 h after catheter removal (Class IIb, level C). The manufacturer suggests that in case of a bloody puncture the next administration of rivaroxaban should be postponed for 24 h (49). The available experience on the use of neuraxial blockade is very limited, as most patients only received single-shot spinal anesthesia or, as neuraxial catheters were removed before treatment was started. As a result, extreme caution is mandatory when using rivaroxaban in the presence of neuraxial blocks (Class IIb, level C).

Apixaban (Eliquis®) is another oral, reversible and selective inhibitor of factor Xa that is related to rivaroxaban and has recently received approval of the European Medicines Agency (EMEA) for postoperative thromboprophylaxis in patients undergoing a total arthroplasty of the knee or the hip. It is even less dependent on the kidney for its

elimination as 75% will be cleared via the hepatic and biliary route resulting in a half-life ranging from 10-15 h (50), with an average of 12.7 h (51). Independent of this longer half-life, it is administered in a twice-daily dose of 2.5 mg. Compared to a twice-daily dose of enoxaparin 30 mg in orthopedic surgery, it has a similar efficacy but with a lower bleeding risk when started 12-24 h postoperatively (52). When compared to a single daily dose of enoxaparin 40 mg after knee and hip arthroplasty, it was associated with lower rates of venous thromboembolism, without increased bleeding (53, 54). As for rivaroxaban, an antidote and a specific monitoring technique are not available yet, but specific anti-Xa assays are under development. Applying the 2 half-lives rule to apixaban would imply that at least 26-30 h should have elapsed since the last dose of apixaban (2.5 mg) and the subsequent withdrawal of a neuraxial catheter (Class IIa, level C). This also means that 1 dose of apixaban should be skipped. Following catheter withdrawal, the next dose of apixaban can be given 6 h later (Class IIb, level C). Similarly to rivaroxaban - and to all new antithrombotic drugs in general - the experience with neuraxial anesthetic techniques, even more so when catheters are considered, is limited. Extreme caution is recommended when using neuraxial blocks in the presence of apixaban (Class IIb, level C).

In the near future, rivaroxaban and apixaban amongst others may replace vitamin K antagonists (VKAs) in the prevention of stroke in the presence of atrial fibrillation and for the acute treatment and secondary prevention of venous thromboembolism. The doses used for these indications are higher than the doses used in prevention of venous thromboembolism (i.e. rivaroxaban 20 mg/day, apixaban 5 mg bid). Thus, the time interval by which these drugs should be interrupted preoperatively to allow for safe surgery should be longer. Because of the large pharmacokinetic variability (i.e. absorption, distribution and elimination) and the influence of patient sex, age, weight and genetic polymorphism) time intervals need to be defined but a delay of 4-5 half lives has been suggested to ensure that there is no or only a minimal residual anticoagulant effect at the time of surgery (55) (Class IIb, level C). In a number of patients, and similar to VKAs, the interrupted treatment may have to be bridged temporarily with UH or LMWH. If a neuraxial block is considered in those patients, the recommendations concerning UH or LMWH apply. In any case, an ongoing treatment with these higher doses of oral direct thrombin inhibitors is an absolute contraindication to neuraxial anesthesia and the presence of an indwelling neuraxial catheter (Class III, level C). Neuraxial instrumentation would only be possible in the absence of any remaining anticoagulant effect of the factor Xa inhibitor used and should preferably be documented prior to any neuraxial instrumentation via an anti-Xa assay calibrated for the specific agent (i.e. anti-Xa activity < 0.1 IU/ml) (Class IIb, level C). Postoperatively, rivaroxaban and apixaban should only be restarted at least 6 h after withdrawal of the neuraxial catheter and taking into account the adequacy of surgical hemostasis (Class IIb, level C).

Direct thrombin inhibitors

Lepirudin

Hirudins are potent anticoagulants with an essentially irreversible bivalent binding to both free and bound thrombin via the active site of thrombin and the fibrinogen-binding site. Although originally prepared as unrefined extracts from leeches, modern hirudins are either recombinants such as lepirudin and desirudin, or analogues like bivalirudin. Desirudin is not available in Belgium while bivalirudin is only (to be) used in patients undergoing a percutaneous coronary intervention although it has also been used to replace UH in cardiac surgery patients with (a recent history of) a type II HIT. Therefore, the latter 2 drugs will not be discussed any further as this is beyond the scope of this chapter.

Lepirudin on the other hand is mainly used in the prevention and treatment of venous thromboembolism in patients with type II HIT. The drug has a half-life of 1.3-3 h, which substantially increases with decreasing renal function. Prophylactic doses range from 10-15 mg twice daily administered subcutaneously. The therapeutic use of lepirudin is started at a dose of 0.1 mg kg^{-1} h^{-1} in the presence of normal renal function and the effect is monitored using the aPTT or the ecarin clotting time (ECT) (56). Finally, hirudins are potentially immunogenic with antibodies developing in 40% of patients. This immunogenicity increases with the duration of the treatment and may prolong the anticoagulant effect (57). Hirudins cannot be antagonized (58).

Once again, there are almost no data on the use of major neuraxial blocking techniques in patients treated with lepirudin, while a case of an epidural hematoma in a patient treated with lepirudin has

been reported (59). Based on the pharmacokinetic data, it is recommended that epidural and/or spinal needle/catheter insertion or catheter manipulation/removal should only be performed at least 8-10 h after the last dose and 2-4 h prior to the next administration (Class IIa, level C). These time intervals only apply to patients with normal renal function and in the absence of antibody formation. A remaining anticoagulant effect should always be excluded through the use of the aPTT or the ECT before any neuraxial manipulation (Class IIa, level C).

Dabigatran

Dabigatran (Pradaxa®) is a novel monovalent direct thrombin inhibitor. The prodrug dabigatran etexilate is ingested orally and converted by plasma esterases into the active dabigatran. The drug is approved for the prophylaxis of venous thromboembolism following elective total hip or knee replacement. Studies indicated that the drug has a prophylactic efficacy and bleeding tendency comparable to that of enoxaparin (60). Dabigatran has a long half-life of 12-17 h and is eliminated mainly via the kidney. An antidote is not available but a number of nonspecific measures such as hemodialyisis or the administration of prothrombin complex concentrate (PCC), Factor eight inhibitor bypassing activity (FEIBA) or recombinant factor VIIa have been used with mixed results (61). The maximum plasma concentration will be reached after 2-4 h. For the prevention of venous thromboembolism after orthopedic surgery, dabigatran is initiated with a dose of 75 mg (creatinine clearance 30-50 ml min^{-1}) or 110 mg (normal kidney function) 1 to 4 h after surgery has been completed. From day 1 postoperatively, the standard dose of once daily 150 mg or 220 mg respectively is administered and repeated every 24 h thereafter. The anticoagulant effect can be quantified using the thrombin clotting time (TT), the ECT or the TT determined by Hemoclot thrombin inhibitor assay (61).

As prophylaxis with dabigatran is started postoperatively, there should be no problem with single-shot neuraxial anesthesia. The experience with dabigatran and indwelling neuraxial catheters is minimal, if not non-existent : the epidural catheters that were used in the studies with dabigatran were all withdrawn at least 4 h before treatment with dabigatran was started. The 12-17 h half-life (in the presence of normal renal function) suggests that a time interval of at least 34 h should be respected between the last dose of dabigatran and catheter manipulation or withdrawal, while the next dose of dabigatran should only be given at least 6 h later. However, the manufacturer recommends that dabigatran should not be used in patients undergoing anesthesia with postoperative indwelling epidural catheters (62) (Class III, level C). This warning may have important medicolegal consequences if a spinal bleeding would develop following the use of an indwelling neuraxial catheter in a patient treated with dabigatran.

Recently, the Committee for Medicinal Products for Human Use of the EMEA adopted a positive opinion on a new indication for dabigatran in the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation. Similar to the oral factor Xa inhibitors, the doses used for these indications are higher than the doses used in prevention of venous thromboembolism (i.e. 220-300 *vs.* 150-220 mg/day). This also implies that a treatment with dabigatran should be interrupted preoperatively for a longer time to allow for safe surgery. These time intervals still need to be defined but, similar to the oral factor Xa inhibitors, a delay of 4-5 half-lives has been suggested to ensure no or only a minimal residual anticoagulant effect at the time of surgery (55) (Class IIb, level C). As is current practice in patients treated with VKAs, the interrupted treatment may have to be bridged temporarily with UH or LMWH. If a neuraxial block is considered in those patients, the recommendations concerning UH or LMWH apply. In any case, an ongoing treatment with higher doses of dabigatran represents an absolute contraindication to neuraxial anesthesia and the presence of an indwelling neuraxial catheter (Class III, level C). Neuraxial instrumentation is only possible in the absence of any remaining anticoagulant effect of dabigatran and should always be documented prior to any neuraxial instrumentation via the use of the TT or ECT (Class IIb, level C). Postoperatively, dabigatran should only be restarted at least 6 h after withdrawal of the neuraxial catheter and taking into account the surgical bleeding risk (Class IIb, level C).

Vitamin K antagonists

Vitamin K antagonists (VKAs), such as acenocoumarol (Sintrom®), phenprocoumon (Marcoumar®) and warfarin (Marevan®), cause the production of dysfunctional coagulation factors II, VII, IX and X, which are no longer capable of chelating calcium, essential for their binding to phospholipid membranes during coagulation.

An uninterrupted chronic and effective therapy with VKAs is an absolute contraindication to neuraxial anesthesia (Class III, level C). When regional anesthesia is deemed necessary, VKA therapy has to be stopped with a delay depending on the half-life of the oral anticoagulant used, the initial INR or PT, and the patient's general condition. In most cases, this treatment will be interrupted perioperatively and temporarily bridged with UH or LMWH (63). Under these circumstances, the specific recommendations for that type of therapy should be applied. With respect to the timing of neuraxial anesthesia and catheter removal, the PT should be above 50% (INR equal to or below 1.4).

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) cause a reversible inactivation of both cyclo-oxygenase I and II, thereby causing platelet aggregation inhibition. The half-life of the NSAIDs used determines the duration of this effect. In contrast, the specific cyclo-oxygenase II inhibitors (i.e. coxibs) do not possess any significant platelet aggregation inhibiting effect (64).

If an NSAID is used as the sole agent interfering with normal coagulation, there are no data available to suggest that there is an increased risk of spinal hematoma formation in patients receiving neuraxial blockade (Class IIb, level C).

Also, there are no data in the literature suggesting that a combination of NSAIDs increases the risk of a spinal hematoma.

Antiplatelet therapy

Dipyridamole

No specific precautions have to be considered if dipyridamole is used as the sole antithrombotic agent (Class IIb, level C).

Low-dose acetylsalicylic acid (i.e. aspirin®)

Acetylsalicylic acid (ASA) produces an irreversible inactivation of cyclo-oxygenase. Low-dose ASA (60-300 mg) mainly inhibits thromboxane A_2 (a potent vasoconstrictor and platelet aggregation stimulator) and not so much prostacyclin (a potent vasodilator and platelet aggregation inhibitor). Overall, low-dose ASA will result in platelet aggregation inhibition that will exceed the last administration of the drug by an entire platelet lifetime (i.e. 7-10 d).

There are no data suggesting that low-dose ASA in isolation is associated with an increased risk of spinal hematoma in the presence of a normal platelet count (Class IIb, level C).

The latter was also true for the combination of low-dose ASA with dipyridamole. However, a study looking at the use of the combination of 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily *vs*. clopidogrel 75 mg once daily for recurrent stroke found a 15% increase in major hemorrhagic events in the patients treated with the ASA-dipyridamole combination (65). In view of these results, it may be wiser to withhold the ASA-dipyridamole combination for 24 h prior to any neuraxial instrumentation (Class IIb, level C). This will allow the additional dipyridamole effect to wear off while the ASA will still remain largely effective.

Ticlopidine / Clopidogrel

The thienopyridines ticlopidine and clopidogrel are prodrugs that are activated by the liver to active metabolites that inhibit adenosine diphosphate (ADP)-induced platelet aggregation through an interaction with the platelets $P2Y_{12}$ receptor and by interfering with platelet-fibrinogen binding. Because of this hepatic conversion, it will take several days before a full antiplatelet effect is reached, although this process is dose dependent (i.e. the higher the loading dose, the faster the onset). The antiplatelet effect is irreversible and cannot be antagonized. Ticlopidine has an elimination half-life of 30-50 h after a single oral dose but up to 96 h after repeated dosing. Clopidogrel has an elimination half-life of 120 h. Because of the irreversible defect in a platelet protein, the platelet inhibition will persist for 7 and 10 d after clopidogrel and ticlopidine cessation, respectively.

Neuraxial anesthesia should be used only if ticlopidine or clopidogrel are no longer active : i.e. administration was stopped for at least 7 d for clopidogrel, and for 10 d for ticlopidine (Class IIa, level C). The next dose of ticlopidine or clopidogrel can be administered after catheter removal. If thienopyridines are used because of the recent implantation of a coronary stent, they should not be stopped only because of the performance of a neuraxial block (Class III, level C). In that case, an interdisciplinary approach including the surgeon, the cardiologist and the anesthetist is mandatory.

Prasugrel

Prasugrel (Efient®) is a new oral third-generation thienopyridine that also produces an irreversible inhibition of platelet aggregation via the platelet $P2Y_{12}$ receptor, which cannot be antagonized. Prasugrel is also an inactive prodrug that is metabolized by the liver into an active metabolite. Compared to clopidogrel, this conversion occurs much faster and more efficiently, and results in a significantly more active compound (66). Thirty to 60 min after oral ingestion, maximum plasma levels will be reached. Elimination of the drug occurs mainly via the kidneys with an elimination half-life of about 7.4 h, but following cessation of treatment, the antiplatelet effect will last 7-10 d (67).

It is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention. It is more efficient than clopidogrel in the prevention of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (68, 69). However, the use of prasugrel may be associated with a higher bleeding tendency. As a result, the manufacturer advises that prasugrel be stopped at least 7 d before elective surgery (70). Considering the higher efficacy and bleeding risk of prasugrel compared to clopidogrel, neuraxial anesthesia should not be performed unless a time interval of 10 d has elapsed since the last dose of prasugrel (Class III, level C). The next dose should be administered 6 h after catheter removal (Class IIb, level C).

Ticagrelor

Ticagrelor (Brilique®) is a pyrimidine and differs from thienopyridines by reversibly binding to the platelet $P2Y_{12}$ receptor and noncompetitively blocking ADP-induced platelet activation (71, 72). Unlike the thienopyridines, ticagrelor does not require metabolic activation. As a result, it has a faster onset of action and less interpatient variability. Ticagrelor has a relatively short half-life of 7-8 h and has to be administered twice daily via the oral route (72-74). Following treatment cessation, platelet function recovers after 4.5 d (75).

The PLATO trial compared the effect of clopidogrel and ticagrelor in patients having an acute coronary syndrome with or without ST segment elevation and demonstrated a significant reduction of risk of death from vascular cause, myocardial infarction or stroke in the ticagrelor group (76-78). The occurrence of major bleeding was similar in both groups, while non-procedure-related bleeding occurred more frequently in the ticagrelor group (75, 77). Ticagrelor was approved in December 2010 for use in the prevention of atherothrombotic events in adult patients with acute coronary syndromes, including patients managed medically and those managed with revascularization. To date, no data are available regarding the perioperative use of ticagrelor. However, the manufacturer recommends that ticagrelor should be discontinued 7 days prior to surgery (79). Therefore, neuraxial anesthesia should only be performed at least 7 d after treatment interruption (Class III, level C). The next dose of ticagrelor should only be administered 6 h after catheter withdrawal (Class IIb, level C).

Glycoprotein IIb/IIIa receptor antagonists

Abciximab (Reopro®), eptifibatide (Integrilin®) and tirofiban (Aggrastat®) represent the strongest form of platelet aggregation inhibiting therapy currently available. By inhibiting the IIb/IIIa receptor, they prevent the binding of platelets to fibrinogen and von Willebrand factor and thus platelet aggregation. Platelet function testing can be used to assess the pharmacodynamic effects of IIb/IIIa receptor antagonists (it is probably a far more effective, but slower, way of assessing platelet aggregation inhibition) (80, 81). The antiplatelet effects are reversible and will disappear spontaneously about 8 h and 24-48 h after discontinuing eptifibatide/tirofiban and abciximab administration, respectively. All glycoprotein IIb/IIIa receptor antagonists, but especially abciximab, can cause a profound thrombocytopenia, which may appear within 1-24 h after the first administration (82-84).

These drugs are only used in acute coronary syndromes for emergency catheterisation, and are often combined with UH and ASA in this setting. In a number of these cases, cardiac surgery will be performed and there will always be a need for prolonged anticoagulation. Therefore, major neuraxial anesthetic techniques should not be used in patients treated with glycoprotein IIb/IIIa receptor antagonists (Class III, level C). If a neuraxial catheter has to be withdrawn after their administration, it should not be performed less than 8-10 h or 48 h after the last dose of eptifibatide/tirofiban or abciximab, respectively and 2-4 h prior to the next administration of these drugs. Also, a platelet count should always be obtained prior to any instrumentation of the patient so as to exclude any thrombocytopenia.

Selective serotonin reuptake inhibitors (SSRIs)

A dysfunction of serotonergic neurotransmission has consistently been found in states of major depression and selective serotonin inhibitors are now often included in its treatment. Serotonin is also involved in platelet aggregation. Selective serotonin reuptake inhibitors (SSRIs) will block the reuptake of serotonin from the plasma by the platelets causing depletion of serotonin in platelets and produce the downregulation of serotonin receptors both in neurons and platelets (85). Overall, the antiplatelet effects of SSRIs cover a whole spectrum of decreased platelet-binding affinity, blockade of platelet calcium mobilization and reduced platelet secretion (86-88). Whether the perioperative administration of SSRIs may cause significant bleeding still remains somewhat controversial, but since the beginning of the 1990s an increasing number of case reports can be found in the literature (89-93). A recent review of the literature found that the risk of upper gastrointestinal bleeding was doubled in patients taking SSRIs when compared to patients taking other antidepressants (94). Also, preoperative SSRI use increased perioperative blood transfusion requirements in orthopedic patients (95) and the need for surgical reoperation because of bleeding after breast surgery (96). In contrast, the preoperative use of SSRIs in patients undergoing coronary artery bypass grafting did not seem to increase the perioperative bleeding risk (97-99). Interestingly, the SSRIs most associated with bleeding are those with the most profound serotonin reuptake inhibition : fluoxetine, sertraline and paroxetine (100). Finally, the SSRI-associated increase in bleeding tendency is mostly seen in patients that were concomitantly treated with antithrombotic drugs such as ASA, thienopyridines, NSAIDs, VKAs and LMWHs (101-105).

Despite their extensive use, there have been no reports of a spinal hematoma following a neuraxial block in the presence of SSRIs. Considering the data that are currently available, the preoperative use of SSRIs does not represent a contraindication to a neuraxial block and no recommendations concerning the preoperative withdrawal of these drugs can be made (Class IIb, level C).

Fibrinolytic therapy

Thrombolytic/fibrinolytic drugs currently available include alteplase (Actilyse®), tenecteplase (Metalyse®), reteplase (Rapilysin®) and urokinase (Actosolv®). These drugs dissolve already formed clots through the activation of the endogenous proteolytic plasmin system. Although the half-lives of thrombolytic/fibrinolytic drugs are relatively short-lasting, their fibrinolytic effects may persist for several days.

Therapy with these agents is an absolute contraindication to neuraxial blockade (Class III, level C). When surgeons or other practitioners insist on the use of these agents when neuraxial techniques have recently been performed, all parties should document this in the patient's records. If a neuraxial catheter was already *in situ* when these drugs were administered – very often in an emergency situation such as a life-threatening pulmonary embolism or a myocardial infarction – it is safer to leave the catheter in place until all thrombolytic effects have disappeared. This can be documented by laboratory values, including fibrinogen levels (and perhaps thromboelastography). If any other antithrombotics, such as UH, are used concomitantly then the recommendations for these drugs do apply.

Herbal medicine

A significant number of surgical patients chronically use herbal medications such as aloe, echinacea, dwarf palm, ephedra, ginger, garlic, ginseng or ginkgo-biloba. The latter three have been linked to an increased bleeding tendency because of an interaction with platelets and VKAs. Still, there is only one report of a spontaneous epidural hematoma associated with the use of garlic (106). In addition, in vivo platelet function was not affected by the administration of garlic, ginkgo or ginseng (107, 108). In summary, there are insufficient data available to decide whether to systematically stop these medications preoperatively or to cancel surgery in patients still treated with these compounds as herbal preparations, by themselves, do not appear to represent an additional significant risk for the development of spinal hematoma in patients having neuraxial anesthesia (10, 109). However, the simultaneous use of these medications with other drugs affecting coagulation such as oral anticoagulants may increase bleeding tendency (Class IIa, level C).

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