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Belgian guidelines concerning central neural blockade in patients with drug-induced alteration of coagulation : An Update

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The first Belgian guidelines on anticoagulants and central neuraxial anaesthesia were published in the year 2000 and intended to give the Belgian anaesthesiologist a framework to hold on to when managing patients treated with anticoagulant drugs (1). Five years later, the time has come to revise these guidelines in view of new information on existing anticoagulants and the appearance of new compounds on the market. The problem posed by the use of anticoagulant drugs in patients receiving central neuraxial anaesthetic techniques remains pertinent. In our aging patient population the use of antithrombotic and anticoagulant drugs for the prevention of arterial and venous thrombosis and/or embolism increases progressively. Finally, the risk of a spinal haematoma cannot be ignored as case reports continue to appear in the anaesthetic literature at regular intervals, substantiating the need for such guidelines.

GENERAL RECOMMENDATIONS

Contributing factors

Routine laboratory investigations do not always detect an impaired coagulation status. A thorough patient history and clinical examination are mandatory to detect an increased bleeding tendency.

Various risk factors such as coagulation disorders, difficult punctures, anatomic abnormalities of the vertebral canal or the spinal cord, and vascular malformations in the vicinity of the spinal cord have been shown to increase the risk of a compressing spinal haematoma after central neuraxial block (2, 3). Several conditions may be associated with altered coagulation. These include the perioperative use of various anticoagulant drugs, low platelet count, renal and/or hepatic failure, chronic alcoholism, chronic steroid therapy, and perioperative infusion of dextrans. The use of large-bore needles, the insertion and removal of catheters, technical difficulties, and bloody or repeated punctures increase the risk of spinal haematoma formation. Therefore, if neuraxial blockade is felt to be beneficial to a given patient, a spinal anaesthetic technique may be a valuable alternative as current data from the literature suggest that spinal puncture may be associated with lesser risk of spinal haematoma than epidural anaesthesia (4).

Spinal haematoma

After neuraxial blockade, all patients should be carefully observed for the possible occurrence of a spinal haematoma. A slow regression of motor- and/or sensory block, back pain, urinary retention, and the return of sensory and motor deficit after a previous complete regression of the block, alone or in combination, suggest a developing spinal haematoma. The use of low concentrations and/or low doses of local anaesthetics for postoperative analgesia will facilitate the detection of a developing haematoma. However, if any doubt persists the epidural infusion of local anaesthetics should be

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stopped immediately in order to detect any neurological deficit as soon as possible. Both patients and nurses should be taught the signs of a spinal haematoma and instructed to contact an anaesthetist immediately.

When a clinical suspicion of spinal haematoma formation arises, an aggressive diagnostic and therapeutic approach is mandatory. This includes an urgent MRI or CT scan and surgery when necessary. A decompressive laminectomy should be performed less than 6-12 h after the appearance of the first symptoms of medullary compression (2, 5).

Thromboprophylaxis

Currently, low molecular weight heparins represent the mainstay in thromboprophylaxis. There are only small differences in efficacy between starting pre- or postoperatively and both options are acceptable (6-9).

Regional anaesthesia itself has some protective effects against the occurrence of thromboembolic complications. Improved pain relief allows earlier mobilisation of the patients. Inhibition of the surgical stress reaction and local anaesthetics alter clotting and fibrinolysis (10, 11). However, it has never been shown that regional anaesthesia by itself increases bleeding tendency (12) or has a thromboprophylactic activity equivalent to or exceeding that of modern thromboprophylactic compounds (13).

Guidelines

These guidelines are not intended to bypass the clinical judgment of the anaesthetist. When the anaesthetist decides not to comply with these guidelines, the rationale to do so should be noted in the patient's chart and informed consent obtained from the patient.

The perioperative cessation of anticoagulant drugs to safely perform a regional block should be discussed with the physician who initiated this therapy and the surgeon. An alternative anaesthetic technique should be used if it is judged that the administration of the anticoagulant must not be interrupted.

The delays mentioned in the present guidelines are only valid in patients with a normal pharmacological profile. This includes a normal hepatic and renal function.

The simultaneous administration of different anticoagulant drugs is not considered. Such combinations may increase the risk of perioperative hemorrhagic complications. Finally, a significant number of surgical patients use alternative or herbal medications such as garlic, ginseng, ginger or ginkgo-biloba preoperatively and perhaps also during their postoperative course. There are insufficient data available to decide to systematically stop these medications preoperatively or to cancel surgery in patients still treated with these compounds as herbal preparations, by themselves, appear to represent no added significant risk for the development of spinal hematoma in patients having epidural or spinal anaesthesia (14). However, the simultaneous use of these medications with other drugs affecting coagulation such as oral anticoagulants may increase bleeding tendency.

The anticoagulant agents that will be discussed in detail hereafter are : low molecular weight heparins, unfractionated heparin, selective factor Xa-inhibitors, anti-vitamin K agents, non-steroidal anti-inflammatory drugs, anti-platelet agents, fibrinolytic/thrombolytic agents, and direct thrombin inhibitors. A list of these drugs with both their generic and registered trade names is included in this text (Table 1).

Low Molecular Weight Heparins (LMWH)

Prophylactic administration

Low-molecular weight heparins (LMWH) are fragments of unfractionated heparin that cause an anti-thrombin III-dependent inhibition of factors IIa and Xa formation. Because of a bioavailability of almost 100% and a half-life of 4-7 h, a once daily dosing is sufficient for thromboprophylaxis. Prophylactic regimens of the different LWMH's currently available are mentioned in table 2.

Since the appearance of the first guidelines in 2000, the attitude towards patients receiving prophylactic doses of LMWH has not changed. An interval of at least 12 hours between the last prophylactic dose of LMWH and subsequent neuraxial blockade should be observed. When prophylaxis is initiated after the procedure, an interval of at least 4 hours should be observed between the performance of the neuraxial technique and the subsequent administration of LMWH.

A neuraxial catheter should not be removed earlier than 12 hours after LMWH administration and at least 4 hours before the injection of the subsequent dose.

Table 1

Generic and registered trade names of anticoagulants currently available in Belgium

	Generic name	Registered trade name
Low-molecular weight heparin	Enoxaparine Dalteparine Nadroparine Tinzaparine	Clexane® Fragmin® Fraxiparine® Fraxodi® Innohep®
Unfractionated heparin	Heparin	Calparine® Heparine Leo® Heparine sodique®
Selective factor X-inhibitors	Fondaparinux	Arixtra®
Anti-vitamin K agents	Acenocoumarol Phenprocoumon Warfarin	Sintrom® Marcoumar® Marevan®
Acetyl-salicylic acid	Acetyl-salicylic acid	Acenterine® Alka Seltzer® Asaflow® Aspegic® Aspirine® Aspro® Cardioaspirine® Cardiphar® Dispril® Sedergine® Tampyrine®
Dipyridamol	Dipyridamol	Coronair® Dipryridamole EG® Dipyridamole Teva® Docdipyri® Persantine®
Acetyl-salicylic acid + Dipyridamol	Acetyl-salicylic acid + Dipyridamol	Aggrenox®
Thienopyridines	Ticlopidin Clopidogrel	Ticlid® Ticlopidine EG® Ticlopidine Teva® Ticlopidin Ratiopharm® Plavix®
Glycoprotein IIb-IIIa receptor antagonists	Abciximab Eptifibatide Tirofiban	Reopro® Integrilin® Aggrastat®
Fibrinolytic/thrombolytic agents	Alteplase Tenecteplase Reteplase Urokinase Streptokinase	Actilyse® Metalyse® Rapilysin® Actosolv® Urokinase Choay® Streptase®
Direct thrombin inhibitors	Lepirudine (Xi)melagatran	Refludan® Exantha® ?

Therapeutic administration

The doses of LMWH used in therapeutic regimens are mentioned in Table 2. A neuraxial block should not be performed earlier than 24 hours after the last therapeutic dose of LMWH. If LMWH treatment is to be maintained following the surgical procedure, only prophylactic doses should be used as long as a neuraxial catheter is maintained. As discussed previously, a neuraxial catheter should not be removed earlier than 12 hours after prophylactic LMWH administration and at least 4 hours before the injection of the subsequent dose. For the first administration of LMWH after neuraxial catheter removal, a prophylactic dose should be used but therapeutic doses may be used subsequently.

Table 2

Prophylactic and therapeutic doses of Low-Molecular Weight Heparins

	Prophylactic doses - SC	Therapeutic doses - SC
Clexane® (enoxaparine)	1 × 20-40 mg*/24 h	2 × 40-80 mg*/24 h (2 × 0.5-1 mg*/kg/d SC or 1 × 1.5 mg*/kg/24 h)
Fragmin® (dalteparine)	1 × 2500-5000 IU PE**/24 h	2 × 5000-7500 IU PE**/24 h (2 × 100-120 IU PE**/kg/24 h or 1 × 200 IU PE**/kg/24 h)
Fraxiparine® (nadroparine)	1 × 2850-5700 IU PE**/24 h	2 × 7500 IE PE**/24 h (2 × 85 IE PE**/kg/24 h)
Fraxodi® (nadroparine)	/	1 × 11400-19000 IU PE**/24 h
Innohep® (tinzaparine)	1 × 50 IU/kg/24 h	1 × 175 IU/kg/24 h

* 10 mg = 10 000 IU AXa (anti-Xa activity)
** 38 IU AXa PE = 41 IU AXa.

Low-molecular weight heparins can induce thrombocytopenia. A platelet count in patients that are or have been on LMWH's for at least 5 days is advised (15).

Unfractionated Heparin (UH) therapy

Therapeutic preoperative use

Unfractionated heparin (UH) produces an anticoagulant effect via an anti-thrombin III-dependent inhibition of factor IIa formation.

Cessation of 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) and should be within normal limits (Table 3). The activated clotting time (ACT) is a point of care test (POCT) that can be used as an alternative to the aPTT. The normal values of both aPTT and ACT will vary from hospital to hospital as they depend upon the specific assay used locally. Unfractionated heparin can induce thrombocytopenia. A platelet count in patients that have been on UH for at least 5 days is advised (15).

Therapeutic intraoperative use

Heparin should not be administered earlier than 1 hour after performing the neuraxial technique.

Although in case of a bloody puncture it may be theoretically safer to postpone surgery, there are no data to support this attitude.

The anaesthetist 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 3) or the ACT are within the normal range and at least 1 hour before any subsequent heparin administration. With current knowledge, the use of neuraxial techniques remains experimental when higher (full therapeutic) doses are to be used (as in cardiac surgery).

Selective Factor X-inhibitors

Fondaparinux (Arixtra®) is a synthetic selective inhibitor of factor Xa formation. With a bioavailability of almost 100% and an elimination half-life of 18-21 h, plasma levels will still be prophylactic after 24 h. The half-life will be prolonged to 36-42 h if the creatinine clearance is below 50 ml/min (16). As a result, fondaparinux should not be used if the creatinine clearance is inferior to 30 ml/min. Fondaparinux is administered subcutaneously once daily in a dose of 2.5 mg and should be started 6-12 h postoperatively (17). The preoperative administration of fondaparinux may even increase the risk of intraoperative bleeding without improving its thromboprophylactic efficacy (18).

Table 3

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.

As this compound is new, there are insufficient data to make recommendations concerning the routine use of neuraxial techniques in patients receiving fondaparinux. However, as fondaparinux is started postoperatively there should be no problem with the preoperative insertion of an epidural/spinal needle for a single-shot anaesthetic technique. In case of a bloody tap, an alternative method of thromboprophylaxis should be considered as insufficient data are available to safely continue the use of fondaparinux. In addition, it is recommended that fondaparinux is not administered along with continuous epidural analgesia (9, 14, 19), but 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 should only be performed under conditions used in the ongoing EXPERT study (GlaxoSmithKline : Evaluation of arixtra for the prevention of venous thromboembolism in daily practice) : i.e. respecting an interval of 36 h after the last dose of fondaparinux and longer if the creatinine clearance is below 50 ml/min. The next dose of fondaparinux should not be administered earlier than 12 h after catheter removal.

Anti-vitamin K agents

Anti-vitamin K agents such acenocoumarol (Sintrom®), phenprocoumon (Marcoumar®) and warfarin (Marevan®) cause the production of deficient coagulation factors II, VII, IX and X which are no longer capable of chelating calcium, essential for their binding to phospholipid membranes during coagulation.

Uninterrupted chronic and effective therapy with these medications is an absolute contraindication for neuraxial anaesthesia. When regional anaesthesia is deemed necessary, anti-vitamin K therapy has to be stopped with a delay depending on the half life of the oral anticoagulant used, the initial International Normalized Ratio (INR) or Prothrombin time (PT), and the patient's general condition. However, most of these patients will temporarily receive another type of anticoagulant (i.e. LMWH, unfractionated heparin or an antiplatelet agent) during the perioperative period. Under these circumstances, the specific recommendations for that type of therapy should be applied. With respect to timing of neuraxial anaesthesia and catheter removal, the PT should be above 50% (INR equal 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 NSAID's used determines the duration of this effect. In contrast, the new specific cyclo-oxygenase 2-inhibitors do not possess any significant platelet aggregation inhibiting effect (20).

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 haematoma formation in patients receiving neuraxial blockade.

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

Antiplatelet therapy

Dipyridamole

No specific precautions have to be considered.

Low dose acetyl-salicylic acid (i.e. aspirin®)

Acetyl-salicylic acid produces irreversible inactivation of cyclo-oxygenase. Low-dose acetyl-

Table 4

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

	Before insertion/removal	After insertion/removal	Other laboratory investigations
LMWH (prophylactic use)	12 h	4 h	Platelet count if LMWH > 5 days
LMWH (therapeutic use)	24 h	4 h	Platelet count if LMWH > 5 days
UH (therapeutic use)	aPTT and/ or ACT within normal range	1 h	Platelet count if UH > 5 days
Fondaparinux	36 h	12 h	
Anti-vitamin K agents	INR $\leq$ 1.4	After catheter removal	
Ticlopidine	10 d	After catheter removal	
Clopidogrel	7 d	After catheter removal	
Eptifibatide / tirofiban	8-10 h	2-4 h	Platelet count
Abciximab	24-48 h	2-4 h	Platelet count
Hirudin	8-10 h	2-4 h	
Melagatran	8-10 h	2-4 h	

salicylic acid (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 acetyl-salicylic acid will result in platelet aggregation inhibition that will exceed the last administration of the drug by an entire platelet lifetime (i.e. 7-10 days).

There are no data suggesting that anti-platelet therapy with low-dose acetyl-salicylic acid is associated with an increased risk of spinal haematoma in the presence of a normal platelet count. This is also valid for the combination of low-dose aspirin with dipyridamole.

Ticlopidine / Clopidogrel

The thienopyridines ticlopidine (Ticlid®) and clopidogrel (Plavix®) inhibit adenosine diphosphate (ADP)-induced platelet aggregation and interfere with platelet-fibrinogen binding. Because of their long half-lives, their platelet aggregation inhibiting effect will persist for 7-10 days after cessation of administration.

Current data are insufficient to assess the safety of combining this therapy with neuraxial techniques. Central nerve blocking techniques should be used only if ticlopidine or clopidogrel is no longer active : i.e. administration was stopped at least 7 days before in the case of clopidogrel and 10 days for ticlopidine.

Glycoprotein IIb-IIIa receptor antagonists

This category of drugs includes abciximab (Reopro®), eptifibatide (Integrilin®) and tirofiban (Aggrastat®) and represents the strongest form of platelet aggregation inhibiting therapy currently available. They not only cause inhibition of ADP-dependent platelet aggregation inhibition, but also of the platelet-fibrinogen and platelet-von Willebrand factor binding. Although the anticoagulant effects can be quantified with the aPTT or the ACT, these tests may not always be a useful indicator of bleeding risk. Platelet function testing is probably a far more effective, but slower, way of assessing platelet aggregation inhibition (21, 22). 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, may cause a profound thrombocytopenia which may appear within 1-24 h after the first administration (23-25). Finally these drugs are often combined with UH and acetyl-salicylic acid in an emergency catheterisation setting.

There are still insufficient data to assess the safety of combining this therapy with neuraxial techniques. Major regional anaesthetic techniques should not be performed in patients treated with these drugs until the anticoagulant effects have disappeared. Based on the pharmacological profile of these compounds epidural and /or spinal needle/ catheter insertion or catheter removal should not be performed less than 8-10 h or 24-48 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.

ANTI-THROMBOTIC / FIBRINOLYTIC THERAPY

Thrombolytic/fibrinolytic drugs currently available include alteplase (Actilyse®),

tenecteplase (Metalyse®), reteplase (Rapilysin®), urokinase (Actosolv® or Urokinase Choay®) and streptokinase (Streptase®). These drugs dissolve already formed clots through activation of the endogenous proteolytic plasmin system. It is the strongest form of anticoagulant therapy available. Although the half-lives of thrombolytic/fibrinolytic drugs are relatively short lasting, their anticoagulant effects may persist for several days.

Therapy with these agents is an absolute contraindication for neuraxial blockade. When surgeons or other practitioners insist on the use of these agents when neuraxial techniques have been performed less than 10 days before their administration, this should be documented by all parties in the patient's records. When a catheter has been inserted, laboratory values, including fibrinogen levels (and perhaps thromboelastography) should be documented to be within normal local limits before removal.

DIRECT THROMBIN-INHIBITORS

Hirudin and (Xi)melagatran

Both hirudins and (xi)melagatran directly inhibit free and bound thrombin. Natural hirudins are anticoagulants that were originally extracted from leeches, but modern biotechnology was able to develop recombinants (also known as r-hirudins) or analogues (i.e. hirulogs). Currently only the recombinant lepirudine (Refludan®) is commercially available in Belgium. Melagatran and its prodrug ximelagatran are synthetic compounds that will become commercially available in the near future. The elimination half-lives of lepirudine (i.v. use), melagatran (s.c. or i.v. use) and ximelagatran (p.o. use) are 2-3 h, 2-3 h and 4-5 h, respectively. Half-lives will be longer in the presence of renal failure. The anticoagulant effect can be quantified using the aPTT or the ecarin clotting time (ECT) (26, 27).

Today, data are insufficient to make any recommendations concerning the use of major nerve blocking techniques in patients treated with lepirudine or (xi)melagatran. Based on the pharmacological profile of these compounds, epidural and /or spinal needle/catheters insertion or catheter removal should only be performed when these drugs are no longer active : at least 8-10 h after last dose of these drugs and 2-4 h prior to the next administration.

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