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CLINICAL REVIEW

A review of pharmacokinetics and relevance to loco-regional anaesthesia of available anti-haemostatic agents in South Africa

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Perioperatively, patients on anti-haemostatic agents present anaesthetists with unique challenges. Besides careful consideration of the overall bleeding versus thrombosis risks, the risks versus benefits of loco-regional anaesthetic techniques must be balanced with the risks of perineural haematoma formation and neurological damage. This article reviews the pharmacokinetics of available anti-haemostatic agents in South Africa in relation to the performance of loco-regional anaesthesia.

Keywords: pharmacokinetics, loco-regional anaesthesia, anti-haemostatic agents

Introduction

Haematoma formation is a catastrophic, albeit rare, complication of loco-regional anaesthesia, with an incidence of 1 in 150 000 in epidural anaesthesia, 1 in 220 000 in spinal anaesthesia, and 0.67% following peripheral nerve blocks (PNBs). The incidence and possible consequences increase in patients on anti-haemostatic agents.[1,2]

The European Society of Regional Anaesthesia (ESRA) classifies PNBs into superficial and deep nerve blocks (DNBs); the latter is associated with an increased risk of haematoma formation in anticoagulated patients, possibly necessitating surgical intervention.[3] Therefore, guidelines for perioperative anti-haemostatic agent use in relation to loco-regional anaesthesia are the same for DNBs and neuraxial anaesthesia.[3] If a combination of anti-haemostatic agents is used, guidelines for loco-regional anaesthesia recommend using the timeframe for the drug with the longest half-life.

Anti-haemostatic agents can be classified as in Figure 1. The drugs in bold are commonly used in South Africa.

Oral anticoagulants

Oral anticoagulants include direct-acting oral anticoagulants (DOACs) and indirect-acting oral agents. DOACs affect clotting factor function, whereas indirect agents affect the production of clotting factors.

Direct-acting oral anticoagulants

DOACs are becoming increasingly popular for non-valvular atrial fibrillation due to their predictable pharmacodynamics, pharmacokinetics, and limited drug interactions.[4,5] DOACs do not require blood test surveillance or bridging therapy with parenteral agents perioperatively. DOACs include the direct thrombin inhibitor, dabigatran, and direct factor Xa inhibitors, namely rivaroxaban, apixaban, and edoxaban (unavailable in South Africa).

In 2021, the possibility of treating patients with venous thromboembolism (VTE) disease with rivaroxaban instead of warfarin was investigated due to the presumed cost-saving of reduced monitoring. However, treating 25 000 patients over

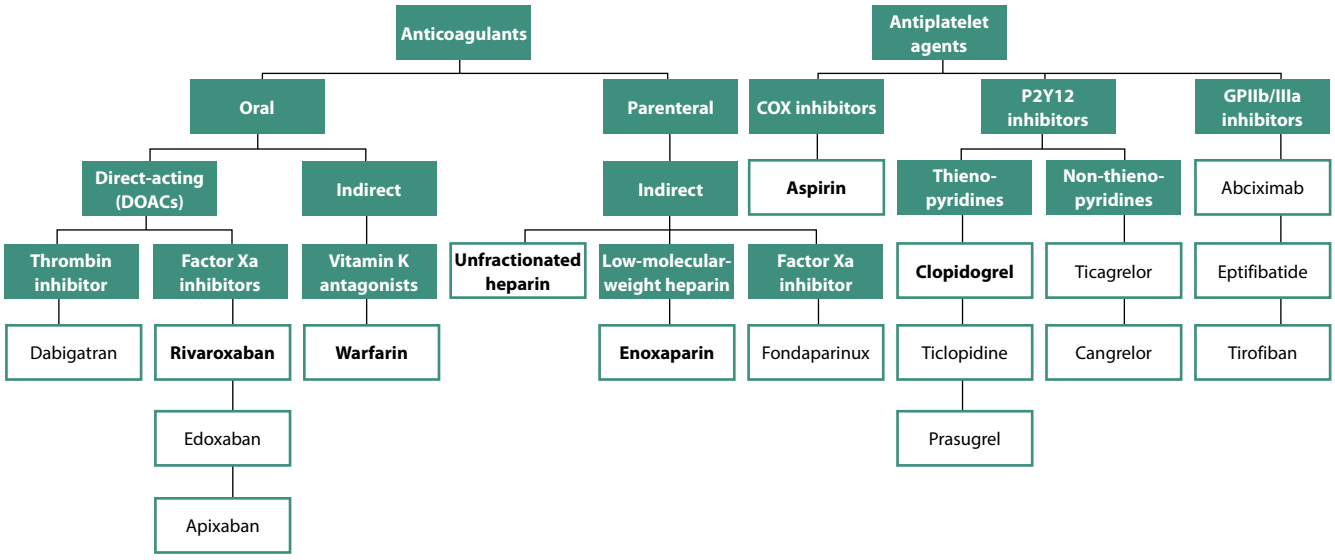

Figure 1: Breakdown of anti-haemostatic agents
COX – cyclooxygenase, DOACs – direct-acting oral anticoagulants, GPIIb/IIIa – glycoprotein IIb/IIIa

12 months with rivaroxaban compared to warfarin and low-molecular-weight heparin (LMWH) resulted in a R122 724 778.49 extra expense. Therefore, if needed perioperatively, warfarin, with a period of bridging with LMWH, is still the recommended method in state practice.[6]

Direct thrombin inhibitors

Dabigatran

Mechanism of action (MOA) and indications: Dabigatran reversibly inhibits free and bound thrombin, preventing the conversion of fibrinogen to fibrin.[7,8] It is indicated in non-valvular atrial fibrillation and VTE prophylaxis.[8]

Pharmacokinetics: In patients with normal renal function, the peak effect is reached within two hours of dosing, and the half-life is eight hours following a single dose or 17 hours after multiple doses.[7,8]

Timeframe: Surgical procedures with a low bleeding risk can proceed 24 hours after the last dose of dabigatran, and procedures with a high risk for bleeding can proceed 48–96 hours later in patients with normal renal function.[8,9]

Neuraxial anaesthesia can be performed 48 hours after discontinuation of dabigatran if the daily dose is less than 220 mg or after 72 hours where the daily dose exceeds 220 mg.[3] Dabigatran treatment may be resumed 24 hours after dural puncture or catheter removal and should not be administered when there is an indwelling catheter.[4] A direct thrombin inhibitor level < 30 ng/ml or a normal thrombin time indicates adequate haemostasis to perform a neuraxial technique in patients with renal impairment with a creatinine clearance (CrCl) ≤ 50 ml/min.[3]

Monitoring: Dabigatran is monitored most accurately through ecarin clotting time (ECT) or thrombin time. It does prolong activated partial thromboplastin time (aPTT), but a ceiling is reached where the dose and aPTT are no longer in a linear relationship.[7,8]

Reversal: Dabigatran is renally excreted and can be removed through dialysis, or its action can be reversed by administering recombinant factor VIIa or idarucizumab, a monoclonal antibody available in South Africa.[7-9] The estimated cost of reversal with idarucizumab is R50 000.[10]

Direct factor Xa inhibitors

Rivaroxaban

MOA and indications: Rivaroxaban is a reversible factor Xa inhibitor, to which it binds directly without using antithrombin III. Rivaroxaban is used in atrial fibrillation, post-transient ischaemic attacks, ischaemic cerebral vascular accidents, and to treat VTE.[9] It is contraindicated in severe liver disease and dose adjustment is necessary in renal failure.

Pharmacokinetics: Rivaroxaban has an oral bioavailability of 80%, with a peak effect at 1–4 hours.

Timeframe: Surgical procedures with low bleeding risk can be performed 24 hours after the last dose of rivaroxaban, and those with a high bleeding risk should ideally be performed 48–72 hours after the last dose in patients with normal renal function.[8,9]

Neuraxial anaesthesia or DNB can be performed 22–26 hours after rivaroxaban discontinuation. In patients with normal renal function, rivaroxaban can be restarted 4–6 hours post-procedure or catheter removal. In patients with impaired renal function (CrCl < 30 ml/min), a period of 30 hours before loco-regional anaesthesia should be adhered to, and catheter removal should only occur 18–24 hours after the last dose.[3,7] In patients taking > 10 mg of rivaroxaban daily, it is advised to wait 72 hours before performing a neuraxial procedure.[3]

Monitoring: Although no long-term monitoring of direct factor Xa inhibitors is required, their function can be monitored with either prothrombin time (PT), aPTT, or Heptest®. Neuraxial techniques can be performed if the DOAC level is < 30 ng/ml or the anti-Xa level is ≤ 0.1 IU/ml.[3]

Reversal: Reversal of direct thrombin inhibitor function is possible with andexanet alfa (Andexxa®), which is a factor Xa decoy protein given as a bolus and followed by an infusion.[8] Andexanet alfa is costly and unavailable in South Africa. Prothrombin complex concentrate (PCC), available as Haemosolvex® in South Africa, can be given at 50 IU/kg for emergency reversal.[9,11]

Apixaban

Timeframe: The guidelines for performing loco-regional anaesthesia in patients on apixaban are the same as for rivaroxaban, except for a 72-hour waiting period after the last dose before neuraxial procedures can be performed in patients taking > 5 mg/day.[3]

Indirect-acting oral anticoagulants

Vitamin K antagonists (VKA), namely warfarin, are the only group in this category.

Vitamin K antagonists (VKA): warfarin

MOA and indications: Warfarin causes competitive inhibition of vitamin K epoxide reductase complex 1, which is required to convert oxidised vitamin K to the reduced form that is a co-factor in the production of vitamin K-dependent clotting factors II, VII, IX, and X.[5,8] Warfarin is the only approved drug for the prevention and treatment of thrombosis in patients with mechanical heart valves and atrial fibrillation.[5,8]

Monitoring: The international normalised ratio (INR) is used to measure the effect of warfarin and predominantly tests factor VII levels, but it is less sensitive to changes in factor II levels.[4,7] An INR level < 1.5 is required for surgical haemostasis, which correlates with approximately 40% of factor VII being present.[4]

Timeframe: Warfarin should be discontinued 4–5 days before elective surgical procedures to allow for clotting factor production and bridging therapy, with LMWH or unfractionated heparin, considered in patients at high risk for VTE.[5] An INR

< 1.5 and a normal PT is required before performing neuraxial anaesthesia or DNB. Indwelling neuraxial or DNB catheters can be removed when the INR is < 1.5.[7] Warfarin can be restarted 24 hours after neuraxial anaesthesia and DNB.[5]

Reversal: The three options for warfarin reversal include Vitamin K, fresh frozen plasma (FFP), and PCC. Vitamin K (1–10 mg) is given intravenously (IV), orally, or intramuscularly for non-life-threatening bleeding due to warfarin use but will promote clotting due to subsequent clotting factor production.[9] In cases of life-threatening bleeding with an urgent need for warfarin reversal, 10–20 ml/kg FFP can be given. PCC is administered in combination with vitamin K at the dosages indicated in Figure 2.[8]

INR	PCC dose
2–4 × normal	25 IU/kg
4–6 × normal	35 IU/kg
> 6	50 IU/kg

Figure 2: PCC dose for reversal of INR
INR – international normalised ratio, PCC – prothrombin complex concentrate

Indirect-acting parenteral anticoagulants

Indirect-acting parenteral anticoagulants include unfractionated heparin, LMWH, and fondaparinux.

Unfractionated heparin

MOA and indications: Unfractionated heparin inactivates factors IIa and Xa by potentiating the inhibitory action of antithrombin III. This prevents fibrinogen conversion to fibrin.[8] It is used for thromboprophylaxis, VTE treatment, and perioperatively for vascular procedures and cardiopulmonary bypass.[8]

Monitoring: Unfractionated heparin efficacy is monitored with either aPTT or anti-factor Xa levels, the former being cheaper and more readily available.[8] Unlike aPTT, which is influenced by factor deficiency or excess and lupus anticoagulant, anti-factor Xa levels are specific to the reagent used. Unfractionated heparin activity can also be measured with an activated clotting time (ACT).[12] Platelet count should be monitored if heparin therapy is continued longer than five days due to the 3% risk of developing heparin-induced thrombocytopaenia.[4,7]

Timeframe: Neuraxial anaesthesia and DNB may be performed in patients requiring IV heparin during a surgical procedure, provided there is a one-hour delay between catheter placement and heparinisation. Catheters may be removed 2–4 hours after the last IV heparin dose and one hour before the next dose. Neuraxial anaesthesia and DNB can be performed four hours after receiving < 200 IU/kg/day subcutaneous heparin, or < 100 IU/kg/day IV heparin.[3,4,7] Heparin infusions should be stopped for 4–6 hours before neuraxial anaesthesia or DNB, and it is recommended that a normal aPTT, anti-Xa level, or ACT be confirmed beforehand.[3,4,13] In patients receiving > 200 IU/kg/day IV heparin, six hours should elapse before neuraxial anaesthesia or DNB is performed, and 12 hours if heparin was given subcutaneously.[3,4,7]

Reversal: Heparin can be reversed with protamine (1 mg per 100 IU heparin) or with 10 ml/kg FFP.[8]

Low-molecular-weight heparin (LMWH)

Enoxaparin

MOA and indications: Enoxaparin irreversibly inactivates factor Xa by potentiating the effects of antithrombin III.[8] The half-life is longer than that of unfractionated heparin and it is used for thromboprophylaxis and thrombosis treatment.[7]

Timeframe: Surgery can be performed 12 hours after discontinuation of prophylactic doses of LMWH (≤ 40 mg/day) and 24 hours after therapeutic doses (1 mg/kg 12-hourly).[9]

Neuraxial anaesthesia and DNB can be performed 12 hours after prophylactic (≤ 40 mg/day) LMWH or after 24 hours if CrCl < 30 ml/min. For therapeutic doses, 24 hours after the last dose should elapse before these techniques are attempted (48 hours if CrCl < 30 ml/min).[3]

Therapeutic LMWH should be restarted no sooner than 24 hours after neuraxial anaesthesia or DNB was performed, and the first dose of therapeutic LMWH can be given 2–4 hours after catheter removal or 24 hours after catheter placement, whichever provides the longer timeframe.[4,7,13] No therapeutic dose of LMWH should be administered while a neuraxial catheter is in situ, although prophylactic doses can be administered 6–8 hours after catheter placement.[3,7]

Monitoring: Anti-factor Xa level is the most accurate way of monitoring the LMWH effect.[8]

Reversal: Protamine can reverse 60% of the effects of LMWH at a maximum dose of 50 mg.[8,9]

Indirect factor Xa inhibitors

Fondaparinux

MOA and indications: Fondaparinux reversibly binds to antithrombin III, and indications for its use are like heparin, making it a valuable alternative in patients that have developed heparin-induced thrombocytopaenia.[8]

Pharmacokinetics: It is administered once daily due to a long half-life of 20 hours. Thus, it should be stopped 24 hours before surgery and cautiously restarted six hours after surgery.[4]

Timeframe: There is limited data on neuraxial anaesthesia and DNB performed in patients receiving fondaparinux. It is suggested to wait a minimum of 24–36 hours before performing neuraxial anaesthesia in patients on ≤ 2.5 mg/day.[4] In patients with CrCl < 50 ml/min, 72 hours should elapse before neuraxial anaesthesia.[3] If > 2.5 mg/day is used, anti-factor Xa levels must be shown to be ≤ 0.1 IU/ml before performing neuraxial anaesthesia.[3]

Reversal: No specific reversal agent is available for fondaparinux, but PCC or recombinant factor VIIa can be considered.[14]

Antiplatelet agents

Antiplatelet agents are classified according to their site of action. Cyclooxygenase (COX) inhibitors work on the thromboxane pathway, P2Y12 inhibitors are adenosine diphosphate (ADP) inhibitors, and GPIIb/IIIa receptor antagonists work on the thrombin pathway.[15]

Cyclooxygenase (COX) inhibitors

COX inhibitors include non-specific COX inhibitors, such as aspirin or ibuprofen, and COX-2 specific inhibitors, such as parecoxib.

MOA: Aspirin irreversibly inhibits COX-1 and 2, preventing prostaglandin A2 production, thus inhibiting platelet function for the lifespan (8–9 days) of the platelet.[8] Alternative non-steroidal anti-inflammatory drugs (NSAIDs) cause reversible inhibition of COX enzymes, and their antiplatelet effect is only sustained 24–48 hours.[4]

Timeframe: Aspirin should be continued perioperatively unless the consequences of bleeding during or after the surgical procedure would be severe, as would be the case with intracranial or spinal surgery.[9]

NSAIDs do not compromise the safety of neuraxial techniques when taken in isolation and if the dose of aspirin is < 200 mg daily.[4,7,8] Should the aspirin dose exceed 200 mg daily, three days should elapse after the last dose, and a normal platelet count should be confirmed before neuraxial anaesthesia is performed.[3]

Thienopyridines

MOA and indications: Thienopyridines bind to the P2Y12 receptor, irreversibly inhibiting the ligand binding properties of the GPIIb/IIIa receptor on the platelet surface.[16] The effect lasts for the lifespan of the platelet. Prasugrel has a more rapid and potent platelet inhibition action compared to clopidogrel and ticlopidine. Clopidogrel and prasugrel are both prodrugs that undergo metabolism in the cytochrome P450 (CYP450) system to the active drug. Thienopyridines are used in patients experiencing acute coronary syndrome, usually after percutaneous intervention and coronary artery stenting.[9]

Clopidogrel

Timeframe: Clopidogrel should be discontinued five days before surgery, and neuraxial anaesthesia and DNB can be performed 5–7 days after treatment discontinuation.[4,8,9] At a dose of 75 mg, clopidogrel may be administered immediately after neuraxial catheters are removed. At a dose of 300 mg, 48 hours should elapse after performing neuraxial anaesthesia or catheter removal. No P2Y12 inhibitor should be given with an indwelling catheter.[3]

Ticlopidine

This drug has fallen out of favour due to the side effects of thrombocytopaenia and neutropaenia.

Prasugrel

Timeframe: Prasugrel should be discontinued seven days before surgery. Neuraxial anaesthesia and DNB can be performed 7–10 days after discontinuation. Treatment may be resumed 24 hours after neuraxial anaesthesia or catheter removal.[7,9,13]

Non-thienopyridines

Ticagrelor

MOA and indication: Ticagrelor is a direct-acting agent that reversibly inhibits the P2Y12 receptor on platelets and is used in treating acute coronary syndrome.[16]

Timeframe: To be entirely free of residual antiplatelet effect, treatment should be discontinued seven days before elective surgery.[4] Treatment may be resumed 24 hours post neuraxial procedure or DNB.[3]

Cangrelor

Due to a very short half-life, cangrelor is only available in IV form. It is currently unavailable in South Africa.[9]

Monitoring: Laboratory tests to monitor antiplatelet drugs are available in South Africa but are complex and not easily accessible.

Reversal: To counteract the action of P2Y12 inhibitors, one or two apheresis units of platelets (pooled platelets) can be transfused. Platelet transfusion is more effective in the reversal of clopidogrel than ticagrelor or prasugrel.[17]

Glycoprotein (GP) IIb/IIIa inhibitors

MOA and indications: GPIIb/IIIa inhibitors are costly, parenterally administered drugs used to reduce ischaemic cardiac events in combination with heparin, and to reduce acute stroke risk in combination with a tissue plasminogen activator.[8]

Pharmacokinetics: They have relatively short half-lives, with abciximab having the longest half-life of four hours.

Reversal: Desmopressin, platelet transfusion, or recombinant factor VIIa administration can be used to reverse the effects of GPIIb/IIIa inhibitors.[15]

Timeframe: Data regarding neuraxial anaesthesia and DNB in patients on GPIIb/IIIa inhibitors is limited. However, these drugs should not be initiated within 4–6 weeks post-surgical procedure.[18]

Abciximab

MOA: Abciximab is an irreversible, high-affinity GPIIb/IIIa receptor antagonist.[19]

Timeframe: It must be stopped 24–48 hours before surgery.[9] Neuraxial techniques and DNB can be performed 48 hours after treatment discontinuation.[4]

Table I: Timeframes for performing loco-regional anaesthesia in patients on anti-haemostatic agents

	Regional procedure	Catheter removal	Restart after procedure	Restart after catheter removal
DOACs				
Direct thrombin inhibitor				
Dabigatran < 220 mg/day	48 hrs[3]		24 hrs[3]	24 hrs[3]
Dabigatran > 220 mg/day	72 hrs[3]		24 hrs[3]	24 hrs[3]
Anti-Xa inhibitor				
Rivaroxaban	22–26 hrs[3,7]	18–24 hrs[3,7]	4–6 hrs[3]	4–6 hrs[3]
Indirect-acting oral anticoagulant				
VKA				
Warfarin	INR < 1.5[7]	INR < 1.5[7]	24 hrs	24 hrs
Parenteral anticoagulants				
Unfractionated heparin				
Heparin IV	4–6 hrs[3]	2–4 hrs after last IV dose[3]	1 hr[3]	1 hr[3]
Heparin S/C	4 hrs[3]		1 hr[3]	1 hr[3]
Low-molecular-weight heparin				
Clexane ≤ 40 mg/day	12 hrs[4,7]	12 hrs[3]	6–8 hrs[3,7]	2–4 hrs[4,7]
Clexane > 40 mg/day	24 hrs[4,7]		24 hrs[3]	2–4 hrs[3,13]
Indirect factor Xa inhibitor				
Fondaparinux ≤ 2.5 mg/day	24–36 hrs[4]			
Fondaparinux > 2.5 mg/day	Anti-Xa ≤ 0.1 IU/ml			
Antiplatelet agents				
COX inhibitor				
Aspirin > 200 mg/day	72 hrs			
P2Y12 inhibitors				
Clopidogrel ≤ 75 mg/day	5–7 days[4,9]		Immediately	Immediately
Clopidogrel 200 mg/day	5–7 days[3]		2 days	2 days
Prasugrel	7–10 days[7,9,13]		24 hrs	24 hrs
Ticagrelor	7 days[4]		24 hrs	24 hrs[3]
GPIIb/IIIa receptor antagonists				
Abciximab	48 hrs[4]			
Thrombolytics				
Streptokinase/alteplase	48 hrs[1]	Normal fibrinogen level		

COX – cyclooxygenase, DOAC – direct-acting oral anticoagulant, GP – glycoprotein, hrs – hours, INR – international normalised ratio, IV – intravenous, VKA – vitamin K antagonists

Eptifibatide and tirofiban (Integrilin® and Aggrastat®)

Timeframe: These drugs should be discontinued four hours before surgery, and neuraxial anaesthesia and DNB can be performed eight hours after treatment discontinuation.[4,7,9,19]

Thrombolytic agents

MOA: Thrombolytic agents cause clot lysis through the action of plasmin. Streptokinase and alteplase have a short half-life and may not directly impact haemostasis. However, there is a knock-on effect of degradation products of fibrin that may impede haemostasis for a longer duration.[1]

Timeframe: Data on loco-regional anaesthesia in patients who received thrombolytic agents is limited. Thrombolytics should not be administered to patients who underwent neuraxial anaesthesia or DNB within the previous 10 days. If a thrombolytic has been administered, at least 48 hours should pass, and normal fibrinogen levels should be documented before neuraxial anaesthesia or DNB is performed.[1]

Conclusion

The risk of perineural haematoma formation versus the benefit of loco-regional anaesthesia in patients on anti-haemostatic agents needs to be individualised according to the recommended timeframes in relation to drug dosing (summarised in Table I).

Conflict of interest

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