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Review Article

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A Narrative Review on Central Neuraxial Blocks and Direct Oral Anticoagulants

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Abstract

Objective

In numerous studies aspiring to clarify when to discontinue direct oral anticoagulants (DOAC) before central nerve blocks (CNB), information about the technique: spinal, epidural, indwelling catheter, multiple attempts, 'bloody tap': is incomplete. This creates difficulty making evidence-based recommendations regarding the safest time frame between the last dose of DOAC and CNB to avoid spinal haematoma. Current guidelines and recommendations are based mainly on pharmacokinetic predictions of the time taken to reach low residual plasma levels of DOAC. Empirical research is almost impossible since the risk of haemorrhagic complication is very low.

Design

A structured search of publications on DOAC and CNB was performed on Pubmed.

Results

Accurate plasma level measurements by mass spectrometry are usually not available. Indirect calibrated anti-Xa and IIa methods are unreliable at DOAC levels <30 ng/ml. DOAC plasma levels that are safe for CNB are presently unknown.

Conclusion

We recommend at least 5 half-lives (T1/2) after the last dose of DOAC before performing CNB, as there is wide interindividual variation in T1/2 and thereby residual plasma concentrations. The maximal residual DOAC plasma level should then be below 3% of therapeutic levels. Such long interruption times prior to surgery are problematic in patients at high risk of arterial and venous thromboembolism, it may be safer to withhold DOAC for 4 half-lives and conduct surgery without CNB. Bridging with low molecular weight heparin (LMWH) may increase the risk of spinal haematoma with CNB.

Keywords: Central Nervous Blockade, Direct Oral Anticoagulants, Spinal Haematoma, Epidural Haematoma, Pharmacokinetics, Epidural Anaesthesia, Spinal Anaesthesia.

1. Introduction

The new/direct oral anticoa1.gulants (NOAC/DOAC) require perioperative awareness of the risk of spinal haematoma [1]. In numerous large DOAC studies, however, information concerning CNB technique is missing or inadequate, which makes it difficult to make evidence-based recommendations regarding how long the interval between the last dose of DOAC and CNB should be, and how much time should pass before DOACs are recommenced after CNB. The orthopaedic studies RECORD 1–4; RENOVATE I–II; REMODEL and RE-MOBILIZE investigated DOAC after knee and hip replacement: low doses of DOAC were initiated first postoperatively to prevent thromboembolic events. Detailed information about which blocks were given is missing [2]. Other studies concerning high-dose DOAC treatment for the prevention of embolic events due to non-valvular atrial fibrillation and treatment of venous thromboembolism (VTE) suffer from the same weakness [3,4,5-10].

This review focuses on the difficulties of laboratory monitoring of DOAC at low plasma concentrations that may still predispose to bleeding complications when the first dose of rivaroxaban is given no earlier than 2xT1/2 (RECORD 1, 2 and 3), or at least 20 h after the procedure (RECORD 4). The next dose of DOAC was given at least 4 h after the removal of the catheter. In the event of a traumatic puncture, defined as more than three attempts or a 'bloody tap', the initiation of DOAC was further postponed by 24 h. A total of 12,729 patients were randomised over the four RECORD studies, of which 8,176 (66%) received a CNB. Starting 12 hours postoperatively, 4086 patients received rivaroxaban per os and 4090 enoxaparin (40 mg) subcutaneously. 1141 patients in the rivaroxaban groups received an epidural anaesthetic (EDA) of which 913 with an indwelling catheter; 2489 a spinal anaesthetic (SPA) and 1048 "other types of anaesthesia" [11,12].

Two CNB-related haematomas were reported: One spinal haematoma was in the enoxaparin group: a 74-year-old woman weighing 41 kg who received 40 mg enoxaparin postoperatively after knee replacement and who required surgical decompression. In this patient, the epidural catheter had been removed 12 h after the last dose of enoxaparin and the next injection was given 6 h after the removal. Creatinine Clearance (CrCl) was later calculated to be 26 ml/min. With such a low body weight and low CrCl there is an increased risk of LMWH accumulation likely contributing to this spinal haematoma [13].

In the rivaroxaban group, there was one spinal haematoma in a patient with traumatic puncture related to spinal anaesthesia prior to knee surgery. This incident was considered mild and not related to the drugs being studied since it occurred before the administration of rivaroxaban.

2. Case Reports of Spinal Haematoma after CNB in Patients Treated with DOAC

Outside the above published studies, 2 case reports in this context have been published. Radcliff et al. reported a 53-year-old woman who received spinal/epidural anaesthesia for knee replacement [14]. No more information about the procedure is given. She commenced 5 mg warfarin on the day of surgery and received 6.5 mg warfarin on postoperative day 1 and 7 mg warfarin on postoperative day 2 when she was discharged. She also received 40 mg enoxaparin on postoperative days 1 and 2. The last doses of warfarin and enoxaparin were on postoperative day 3. On postoperative day 4, she was switched to rivaroxaban (dose not given) by an outpatient physician. On the sixth day, Magnetic resonance imaging (MRI) verified a spinal haematoma that was surgically evacuated. The MRI also verified a severe lumbar spinal stenosis. Routine coagulation analyses were normal but clinical examination verified extensive ecchymoses on the buttocks and thighs.

2.1 Comment: A coagulopathy caused by the combination of LMWH, warfarin and rivaroxaban is the most probable cause of this patient's spinal haematoma, although spinal stenosis may have been a contributing factor.

Burjorjee et al reported an 89-year-old woman undergoing upper abdominal surgery, who received rivaroxaban due to atrial fibrillation and previous hemiparesis. Rivaroxaban was discontinued 4 days preoperatively [15]. A thoracic epidural was placed at T8/9 immediately prior to induction. Venous thromboembolism prophylaxis was provided with compression devices, and twelve hourly unfractionated heparin initiated 5.5 hours after epidural placement. On postoperative day 2, the patient was noted to have a bilateral motor block, and imaging demonstrated a thoracic epidural hematoma extending from T6 to T11.

2.2 Comment: Preexisting neurological deficits may have delayed detection

Probably there are more unreported cases as registration of "all" types of perioperative complications is an emerging field. Also, we only searched for Pubmed-registered case reports. Bleeding complications after CNB have hitherto at least in Sweden better been found in registrations of malpractice lawsuits or insurance reimbursements. In addition, "spontaneous" spinal haematomas can occur in patients with DOAC irrespective of CNB procedures.

3. Laboratory Monitoring of DOAC

The most accurate method to determine the concentration of DOAC in plasma is mass spectrometry (LC-MS/MS). This method is only offered at one hospital laboratory in Sweden (Clinical Pharmacology, Karolinska Hospital, Stockholm). Tests of residual DOAC effect are offered primarily at university hospitals using plasma-based tests such as the anti-Xa activity assays (calibrated for apixaban, rivaroxaban, edoxaban), diluted thrombin time (dTT-HemoclotTM), ecarin-based assays (ECT/ECA) or anti-IIa activity

assay (for dabigatran) [16-18]. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) are not recommended for determining whether it is safe to perform CNB. A normal aPTT merely excludes supratherapeutic dabigatran levels and a normal PT-INR excludes supratherapeutic Xa-inhibitor levels.

Anti-Xa activity <0.1 U/ml is considered safe for CNB, but this refers to a method calibrated with unfractionated heparin or LMWH. For measurement of factor-Xa-inhibiting DOAC, the anti-Xa activity method needs to be calibrated with the drug being measured [19]. Anti-Xa activity corresponds well to both high and low levels of DOAC (apixaban, rivaroxaban and edoxaban), but is still less reliable for plasma levels <30 ng/ml when compared to mass spectrometry, since it is close to the detection limit of the methods [20]. There is however data on measurement of Xa-inhibiting DOACs with a heparin-calibrated assay and LC-MS/MS, with a suggested decision limit of 30 ng/ml [19]. Corresponding studies of monitoring dabigatran have shown that the most widely used dTT assays are not sensitive in the low range unless specific calibrators are used, but still unreliable at <30 ng/ml. TT and ECT/ECA assays appear to be better alternatives but, have not been evaluated in this clinical context [20]. Douketis et al. found a correlation (r = 0.86) for dTT and concentrations of dabigatran in plasma. Special calibrators for concentrations <50 ng/mL of dabigatran, are being developed, with a correlation of 0.84 [21]. There is still too much inaccuracy linked to these methods in the lower concentration ranges of DOAC, and thus more studies, faster and better methods are needed [22]. One option could be to use viscoelastic hemostatic assays such as ROTEM with a Xa-based trigger [23].

4. DOAC Half-Lives (T1/2) and Residual Plasma Concentrations to Safely Perform CNB

When DOAC treatment is discontinued, an approximate 10% residual concentration of the drug is achieved after three times the half-life (T1/2) [24,25]. Large individual differences have been shown, both after single doses and after continuous treatment, for dabigatran and rivaroxaban. Variations >60% have been seen, reflecting the significant variations in pharmacokinetics and drug elimination for the different DOACs [6].

Safe levels of residual DOAC plasma concentrations for CNB were unknown until the the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial [26]. From the PAUSE register, Shaw et al. identified patient characteristics associated with elevated residual perioperative levels of apixaban, dabigatran and rivaroxaban after standard DOAC specific interruption intervals [27]. In patients with low bleed-risk, residual DOAC levels were raised in women, age ≥75 years, CrCl <50 mL/min and DOAC interruption times <36 h. In patients with high bleed-risk, women had higher preoperative residual DOAC levels. The residual plasma concentration of dabigatran recommended by the European Medical Agency (EMA) prior to surgery (not specifically for CNB) is 48 ng/ml, which corresponds to >75% elimination of dabigatran [28]. This is usually attained after 2xT1/2 in healthy individuals. Dincq et al. recommends 1–2 additional half-lives to avoid prolonged dTT or elevated plasma concentrations of DOAC at the day of surgery while the European Societies of Anaesthesiology and Intensive Care/-Regional Anaesthesia (ESAIC/ESRA) recommend that 'neuraxial procedures should coincide with the lowest anticoagulant level' [26, 29].

The American Society of Regional Anesthesia and Pain Medicine recommends an interval of 5 T1/2 to allow complete elimination between stopping oral anticoagulants and carrying out medium or high-risk pain procedures [30]. Due to the variability in DOAC metabolism and elimination, this interval corresponds to 4–5 days for dabigatran, and 3 days for rivaroxaban and apixaban. This recommendation has also been adopted by the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, the World Institute of Pain, French Working Group on Perioperative Hemostasis and the European Heart Rhythm Association Hemostasis (GIHP) [31-33].

Douketis et al. recently commented on the latest ASRA guideline. With the high inter-individual variability of DOAC plasma concentration they warned that estimating the elimination T1/2 of DOACs using the glomerular filtration rate is not sufficient to determine the required interval before neuraxial anesthesia [34]. They suggested that the ideal timing of stopping DOAC treatment should be based on residual plasma concentration measured in the perioperative setting. Douketis et al. and Goudier et al. have demonstrated high DOAC plasma concentrations in two multicenter studies [35,36].

5. Renal and Liver Effects

The kidneys and liver eliminate DOAC to different extents depending on the drug, which affects the required preoperative withdrawal of the drugs and the estimated safety of performing CNB (see below for guidelines and recommendations). Renal and hepatic failure in themselves affect coagulation, regardless of DOAC treatment (see below). For this reason, it has been argued that 5xT1/2, when treated with the lowest dose of DOAC seems to be the safest approach (Table 1, Figure 1) [37-39]. Then, approximately 3% of the DOAC remains.

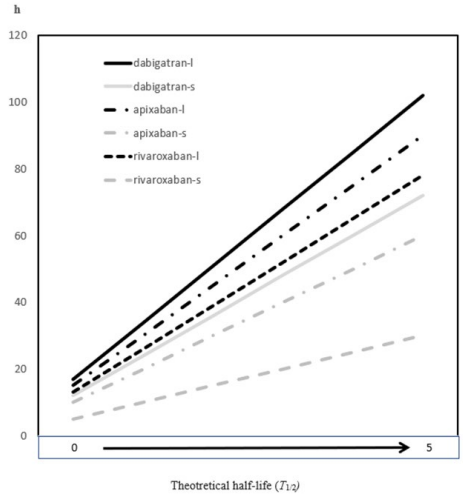

Figure 1. The shortest (S) and longest (L) half-lives ($T_{1/2}$) (y-axis (h)) and 1, 2, 3, 4 and 5 theoretical $T_{1/2}$ (x-axis) for 3 different DOACs.

***4x*$T_{1/2}$ - dabigatran: $T_{1/2}$ 12–17 h = 68 h withdrawal, prolonged if GFR<50mL/min)**
***4x*$T_{1/2}$ - rivaroxaban: $T_{1/2}$ 5–9 h, 11–13 h in the elderly = 52 h withdrawal**
***4x*$T_{1/2}$ - apixaban: $T_{1/2}$ 10–15 h = 60 h withdrawal**
***5x*$T_{1/2}$ - dabigatran: $T_{1/2}$ 12–17 h = 85 h withdrawal, prolonged if GFR<30mL/min**
***5x*$T_{1/2}$ - rivaroxaban: $T_{1/2}$ 5–9 h, 11–13 h in the elderly = 65 h withdrawal**
***5x*$T_{1/2}$ - apixaban: $T_{1/2}$ 10–15 h = 75 h withdrawal**

Table 1. Withdrawal of DOAC prior to CNB based on $T_{1/2}$ ranges and then counted on the maximal half-lives (T1/2) for 3 different DOACs.

6. Drug Interactions

Drug interactions may prolong DOACs' $T_{1/2}$ – for example dabigatran's $T_{1/2}$ is prolonged by verapamil, amiodaron and clarithromycin [40]. Information in Table 1 is based on maximal T1/2 and the reasoning for the interruption of DOAC prior to CNB, as mentioned above.

7. Guidelines

National and international peer-reviewed published guidelines differ. Some of these guidelines are presented in Table 2. From these and our review we recommend 5x$T_{1/2}$ after last dose of DOAC and the CNB procedure. A recent guideline from neurologists in the UK recommends much shorter withdrawal time for diagnostic lumbar punctures [41].

	T ½ (h)	ASRA	ESA	SSAI	PRAP DK
dabigatran	**12–16**	**96–144**	**34**	**48**	**75**
apixaban	**8–15**	**72–120**	**26–30**	**48**	**40–75**
rivaroxaban	**5–13**	**72**	**Ca 24**	**48**	**25–65**

Table 2. Different recommendations for time interval (h) between last dose of DOAC and CNB procedure. ASRA (American Society of Regional Anesthesia), ESA (European Society of Anaesthesia), SSAI (Scandinavian Society of Anaesthesia and Intensive Care); PRAP (Perioperativ regulering af antitrombotisk behandling, Danish Society of Thrombosis and Haemostasis (DSTH).

8. DOAC Antidotes

Idarucizumab (Praxbind®) completely reverses the effect of dabigatran for emergency use. Andexanet-Alfa (Ondexxya®), recently approved by the FDA, is a reversal agent for rivaroxaban, apixaban and edoxaban [40]. This drug has recently been granted conditional marketing authorization in the EU. The preliminary price for this antidote is very high: 16-32 000 USD, whether this cost can be balanced against all costs of not reversing severe DOAC emergency bleedings is debatable [42]. The published studies have been very strict, only involving small intracranial hematoma <60

ml at the initial CT scan and Glasgow Coma scale >7.

Four-factor prothrombin complex concentrate (PCC) reverses some of the effects of DOACs [43,44]. This is standard treatment in many situations to control bleeding in emergency surgery but has not been reported for optimization of haemostasis before CNB in patients with insufficient withdrawal of DOAC or in emergency situations. Another choice is activated PCC (Feiba®), that has been used in in vitro trials of DOC reversal – but there is little clinical experience of this drug in DOAC reversal other than in intracerebral bleeding [45]. Fibrinogen concentrate, antifibrinolytics and oral charcoal, respectively, can be considered as additional measures. Massive blood loss and thrombocytopenia should be treated independently according to local guidelines for transfusion of blood and blood products.

9. Discussion

One must be aware that interrupting thromboprophylaxis prior to surgery increases the risk of arterial and venous thromboembolism, especially in high-risk patients. This category of patients requires extra attention, and it is recommended that anticoagulation and its interruption be discussed with physicians with expertise in coagulation. Knowledge of thrombosis risk scores such as CHA2DS2-VASC and bleeding risk scores such as HAS-BLED is necessary, as is an awareness of which anaesthetic options are available: the RELY studies showed that the risk of developing a stroke increased when the plasma concentration of dabigatran decreased under 28 ng/ml while the risk of surgical bleeding at this concentration area was low [43,44].

Since the early preoperative interruption of DOAC entails risks to the patient, one could argue that the concentration of DOAC should be monitored. If the results show low values, then surgery should not be postponed further. It should be noted that the concentration limit at 30 ng/ml might have been suggested because DOAC specific laboratory tests become unreliable under this level [27]. However, the safety aspects of CNB procedures in this context is generally not discussed. Prolonging interruption of DOAC to safely perform CNB will increase the risk for thromboembolism, bridging with a LMWH to decrease the thromboembolic risk could increase the risk for CNB related spinal haematoma with low plasma levels of DOAC. As discussed above, whether to bridge or not should be discussed with experts [46]. Patients at low to moderate risk of thromboembolism should not be bridged when the length of time without thrombosis prophylaxis is less than 96 h [47]. For patients at high risk for thromboembolism, individual patient and surgical factors need to be considered before the decision to bridge is made. The benefit of bridging patients who have a considerable risk of bleeding (as with CNB) may or may not outweigh the benefits. Since there is little data concerning bridging procedures and different DOACs, randomized studies on periprocedural management of NOACs are urgently needed [48, 49].

Recommendations concerning the timing of the first dose of DOAC after a single-dose SPA/EDA without a catheter, or after removal of an epidural catheter, are based on the theoretical reasoning that without coagulopathy it takes about 6–8 h for a patient to form a clot and that maximal effect (Cmax) after oral administration of DOAC is achieved in 2–4 h [31,50,51]. Therefore, the current recommendation is to wait 4–6 h after surgery for reintroduction of DOAC. One should consider that individual differences in perioperative bleeding, transfusions and high-risk surgery might make this recommendation unsafe. If an epidural haemorrhage should occur when the epidural catheter is being removed (which would go unnoticed until any compression-related symptoms presented themselves), postponing reintroduction or initiation of DOAC would most likely be recommended.

Usually, there is no reason to postpone surgery due to the occurrence of bleeding during the CNB procedure. However, reintroduction or initiation of treatment with dabigatran or rivaroxaban should be postponed until 24 h after surgery [38,39]. There is no available information concerning apixaban or edoxaban or ‘bloody tap’.

Research concerning DOAC and indwelling epidural catheters is almost non-existent. The studies touching on this subject all describe catheters that were removed at least four hours before treatment with dabigatran was initiated. At least one manufacturer of epidural catheters (Boehringer-Ingelheim) does not endorse treatment with dabigatran in patients with indwelling epidural catheters, which of course leads to medicolegal difficulties in the event of a spinal haematoma [28]. If treatment with dabigatran is unintentionally initiated in a patient with an indwelling catheter with no other risk factors, 2xT1/2 is probably a reasonable approach - but 3–4 days (5xT1/2) between the last dose of dabigatran and removal of the catheter is most likely a safer choice (Table 1). Eriksson et al. recommend postponing removal of the catheter until 36 h after the last dose of dabigatran and waiting another 12 h after the removal before reintroducing the drug [6].

The EMA recommends at least 18 h between the last dose of rivaroxaban and removal of an epidural catheter and at least 6 h before reintroducing the next dose [52]. European Society of Anaesthesiology (ESA) guidelines advocate a longer interval (22–26 h) between the last dose of rivaroxaban and the removal of the catheter depending on the reduction of renal function and the prolongation of T1/2 often seen in older patients (11–13 h) [4]. ESA and ESAIC/ESRA recommend a DOAC-free interval of 4–6 h after removing an epidural catheter before reintroducing the drug [27].

Application of the same regime for apixaban means a time frame of 20–30 h between the last dose of apixaban (2.5 mg) and removal of the epidural catheter. Coverage of apixaban and CNB is incomplete [53].

10. Conclusions

The anaesthesiologist in charge should conduct an individualised evaluation of whether CNB is safe in the current the situation and specific patient. Choice of anaesthetic method must be made in consultation with the surgeon and taking into consideration the possibilities of surgical haemostasis and the level of thromboembolic risks. The surgeon should have discussed this with a coagulation expert when planning DOAC interruption. With this information in mind, the decision of preoperative withdrawal from any anti-haemostatic drugs - and the reintroduction of the same - can be made. Unfortunately, CNB safety is not always in the mind of the surgeon or the coagulation expert! It is important to evaluate the benefits and possible risks when deciding whether to perform a CNB – general anaesthesia is usually an option. An increased risk of bleeding is associated with multiple puncture attempts and large bore needles, so the smallest needle size possible should be used. Skilled and experienced anaesthesiologists should perform CNB in patients treated with DOAC.

In cases where residual DOAC effect is suspected or likely, general anaesthesia is recommended. In most cases, there is little to no evidence of reduction of morbidity/mortality favouring CNB over general anaesthesia. In this review, we recommend 5 half-lives (maximal T1/2: dabigatran 85h; (4 days), rivaroxaban 65h; (3 days) and for apixaban 75h; (3 days)) after the last dose of DOAC when performing CNB, as there is a wide interindividual variation in T1/2 and residual plasma concentrations. Bridging with low molecular weight heparin is generally not needed after DOAC cancellations up to 96 hours – thus not needed in the defined time intervals above. Bridging procedures with LMWH can have additive anticoagulative effects on low DOAC levels even after 5xT1/2 and increase the risk for CNB related spinal haematoma and surgical bleeding in surgery with high risk for bleeding complications. In patients at high-risk of thrombosis, cancellation more than 2xT1/2 increases perioperative thromboembolic events: CNB is not recommended in these patients. With decreased renal and liver function and drug interactions increasing the anticoagulative effect of DOAC and decreasing their elimination, longer preoperative DOAC cancellation-times are needed. A minimum time frame of 6h between CNB, usually single-shot SPA or removal of an epidural catheter, and the next dose of DOAC is recommended.

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