On the Treatment of New Oral Anticoagulant-Associated Gastrointestinal Hemorrhage


ABSTRACT

The recently introduced new oral anticoagulants (nOAC) carry a higher gastrointestinal bleeding risk compared to traditional antithrombotic therapy. Current diagnostic coagulation tests are not accurate enough to determine the level of coagulopathy. Besides that, the lack of a specific antidote leaves the endoscopist unsure how to achieve hemostasis during gastrointestinal hemorrhage. In this brief report, we address the (endoscopic) management, when facing a suspected nOAC-associated gastrointestinal hemorrhage. We recommend that specific coagulation tests such as diluted thrombin time and anti-Xa measurement should be made available. Furthermore, nOAC should be stopped. Finally, correcting coagulopathy with administration of prothrombin complex concentrate, recombinant factor VIIa and even hemodialysis should be considered, whereas fresh frozen plasma and vitamin K have no place. The generalizability of these recommendations needs to be confirmed in future studies.

Key words: new oral anticoagulant – dabigatran – rivaroxaban – apixaban – gastrointestinal bleeding – antidote management – coagulopathy

Abbreviations: aPTT: activated partial thromboplastin time; DDAVP: desmopressin; dTT: diluted thrombin time; DVT: deep vein thrombosis; GI: gastrointestinal; INR: international normalized ratio; LMWH: low-molecular-weight heparin; nOAC: new oral anticoagulants; NSAIDS: non-steroidal anti-inflammatory drugs; PE: pulmonary embolism; PCC: prothrombin complex concentrate; PT: prothrombin time; TT: thrombin time; VKA: vitamin K antagonist.

INTRODUCTION

With the advent of the new oral anticoagulants (nOAC), endoscopists face a novel and potent adversary. NOAC are increasingly being considered to replace standard treatment for indications such as thromboprophylaxis during orthopedic surgery, prevention of thromboembolic complications in patients with atrial fibrillation, but also treatment for pulmonary embolism (PE) and deep vein thrombosis (DVT) [1]. In addition to their equal or even improved efficacy over current drugs such as vitamin K antagonists (VKA) and low-molecular-weight heparin (LMWH), a possible advantage of nOAC includes the lack of repetitive blood testing to dose within therapeutic levels [1]. Currently, three nOAC have reached phase IV clinical trials, i.e. dabigatran (Pradaxa® Boehringer-Ingelheim Pharma GmbH, Germany), rivaroxaban (Xarelto® Johnson & Johnson/Bayer HealthCare, Germany) and apixaban (Eliquis® Bristol Myers Squibb/Pfizer, UK) [1]. Dabigatran is a direct thrombin (factor IIa) inhibitor, whereas the latter two are factor Xa-inhibitors. As these drugs have novel targets within the coagulation cascade, current coagulation tests, such as international normalized ratio (INR) are not accurate and, moreover, no antidote is available thus hampering proper management in case of bleeding. Furthermore, drug-drug interactions and renal impairment may lead to increased blood levels of these drugs, resulting in a higher bleeding risk.
This brief technical report addresses the (endoscopic) management, when facing a suspected nOAC-associated gastrointestinal (GI) hemorrhage.

**EPIDEMIOLOGY OF nOAC ASSOCIATED GI HEMORRHAGE**

The impact of nOAC on gastrointestinal hemorrhage is yet unknown, but substantial evidence for an increased risk can be derived from reviewing the current available data of the phase II/III studies covering more than 150,000 patients [2]. The incidence of upper GI bleeding in the general population is relatively low, counting 1 per 1000 person-years [3]. The use of nOAC compared to standard anticoagulant therapy leads to a 30% increase in GI hemorrhage on top of the 2 to 3-fold increased GI bleeding risk compared to non-use [3, 4]. More than ten million persons in Europe and North-America are estimated to require anticoagulant therapy and may switch to nOAC in the near future [5]. Therefore, a small but significant absolute risk excess will have major implications for the overall GI bleeding incidence.

**INITIAL MANAGEMENT OF SUSPECTED nOAC ASSOCIATED GI HEMORRHAGE**

As a recent international consensus on the management of GI bleeding recommends, no time should be lost correcting VKA-induced coagulopathy before starting early endoscopy [6]. However, it is not known if the use of nOAC, in contrast to VKA, predisposes to prolonged bleeding or rebleeding. Standard coagulation tests such as activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) are used as a screening tool [7]. However, endoscopists should realize that these routine coagulation tests are highly reagent dependent and that normal INR and aPTT results do not rule out the presence of therapeutic anticoagulant levels. Each laboratory should test the sensitivity of their assays to nOAC [8]. Specific tests such as diluted thrombin time (dTT) for dabigatran and anti-Xa measurement for rivaroxaban and apixaban can measure accurately the level of anticoagulation (i.e. level of concentration in blood) [9]. The availability of these tests varies between laboratories and this should be checked in advance. However, no reports have yet been published on the exact nOAC concentration range and the risk of GI hemorrhage.

**ENDOSCOPIC AND PHARMACOLOGICAL MANAGEMENT OF nOAC ASSOCIATED GI HEMORRHAGE**

Concerning endoscopic management, no data are available regarding other endoscopic strategies than currently used. Antithrombotic agents may precipitate and prolong bleeding from pre-existing lesions despite current hemostatic techniques [4]. Novel endoscopic modalities such as hemostatic powder may thus prove a welcome alternative when dealing with nOAC-associated bleedings [10].

No data on the protective effect of proton pump inhibitors (PPIs) during nOAC use are currently available. However, in the case of nOAC-associated upper GI bleeding, intravenous administration of high dose PPIs is presumably beneficial, as it neutralizes pH which leads to the stabilization of the blood clot [6].

**CORRECTING COAGULOPATHY DURING nOAC ASSOCIATED GI HEMORRHAGE**

Supratherapeutical ranges of drug induced coagulopathy during GI bleeding are associated with increased mortality [11]. Correcting nOAC induced coagulopathy should thus be the goal; however, no specific antidote against dabigatran or rivaroxaban or apixaban is available. The current available measures to restore coagulation have not been tested in bleeding patients on nOAC in a controlled experimental setting. Some recommendations can be made based on limited clinical experience and studies in healthy volunteers and animals (Table I).

- **a. Stopping the nOAC.** This can be considered for every patient experiencing GI hemorrhage while using nOAC. The decision to discontinue nOAC therapy in the setting of acute bleeding should be made on an individual basis, carefully weighing the thromboembolic and gastrointestinal risks [6]. The nOAC induced coagulopathy is quickly recovered after stopping (11/2 9-14 hrs depending on renal clearance). In addition, within 2-4 hours after restarting nOAC, the therapeutic effect is restored. The latter is of importance given the increased mortality when stopping anticoagulants compared to continuation after GI hemorrhage [12]. Switching to VKA therapy in these patients might be a safer option and should be considered.

- **b. Prothrombin complex concentrate (PCC).** Some evidence exists that the administration of PCC may act as a reversal agent in healthy humans using nOAC [13, 14]. Whether the recovery of coagulopathy is also paralleled by hemostasis remains to be observed. Nevertheless, administration of PCC (25-50 IU FIX/kg i.v.) is to be considered in case of severe nOAC-associated GI hemorrhage.

- **c. Fresh frozen plasma.** Although commonly used, no data exists of humans taking nOAC. Scant data in animal models argue against recommendation [15].

- **d. Recombinant factor VIIa.** Its use has not been studied in humans for reversal of nOAC and the results in animal models are inconclusive [15]. In cases of severe nOAC-associated GI

### Table I. Summary of recommendations for managing significant nOAC-associated gastrointestinal hemorrhage

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<th>Recommendations</th>
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<tr>
<td>1. Supportive care such as restrictive blood transfusions</td>
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<td>2. Determine level of coagulopathy</td>
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<tr>
<td>3. Stop nOAC, and consider switch to VKA after hemostasis</td>
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<td>4. Endoscopy; as commonly performed, consider i.v. PPI</td>
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<td>5. In severe bleeding; consider PCC (also DDAVP, tranexamic acid)</td>
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<tr>
<td>6. In uncontrollable bleeding; consider recombinant factor VIIa, hemodialysis</td>
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nOAC: new oral anticoagulants; VKA: vitamin K antagonist; PCC: prothrombin complex concentrate; DDAVP: desmopressin
hemorrhage, the benefit-to-costs-and-risks-balance should be weighed per person. No experimental evidence is available for desmopressin (DDAVP) and antifibrinolytic agents such as tranexamic acid. A raised concern for the possibility of a tromboembolic event was recently waived after a Cochrane review showing no increased risk on myocardial infarction, stroke, DVT or PE [16].

e. Hemodialysis or hemoperfusion. Whereas rivaroxaban and apixaban are too highly protein bound to be effectively removed by these methods, dabigatran is the only appropriate candidate [17]. Unfortunately, performing this in a bleeding patient in a hypovolemic shock may be, at least, challenging.

CONCLUSION

In light of the absence of reports on the outcome of nOAC-associated GI-bleedings, endoscopists should be prepared to deal with such bleedings given the increased risk of hemorrhage. Accurate determination of coagulopathy by specific coagulation tests such as dTT and anti-Xa measurement, stopping nOAC, considering PPI administration and achieving hemostasis with products such as PCC will have to be included in the endoscopist’s toolkit. Careful surveying and reporting on nOAC-associated GI hemorrhage will clarify the remaining areas of uncertainty.

Conflicts of interest: The authors declare that they have no competing interests.

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REFERENCES