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Review

Management of novel oral anticoagulants in emergency and trauma surgery

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ABSTRACT

Background: The compelling safety, efficacy and predictable effect of novel oral anticoagulants (NOACs) is driving a rapid expansion in their therapeutic indications. Management of the increasing number of patients on those new agents in the setting of emergency or trauma surgery can be challenging and the absence of specific reversal agents has been a matter of concern. This review summarises the key principles that underpin the management of those patients with a particular emphasis on the recent development of specific antidotes.

Findings: As of 2015, a new line of antidotes, specific for these drugs, are at different stages of their development with their release imminent. However, as NOACs are innately reversible due to their short half-life, the use of reversal agents will probably be restricted to a few exceptional cases. Post-marketing surveillance will be paramount to better clarify the role of these promising drugs.

Conclusions: Management of patients on NOACs in the context of emergency or trauma surgery relies on best supportive care in combination with the blood products and/or specific antidotes as required. Familiarity with the new reversal agents is essential but further evidence on their indications, safety and efficacy as well as consensus guidelines are warranted prior to widespread adoption.

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Introduction

Anticoagulation using vitamin K antagonists (VKA) is the conventional treatment and prevention of thromboembolic disorders, though these are constrained by the need for monitoring and their drug interactions. Therefore, these are

gradually being replaced by an emerging class of drugs termed novel oral anticoagulants (NOACs).

Two classes of NOACs are currently available, which exert their effects through inhibiting factor Xa or factor IIa/thrombin (Fig. 1).¹ These are as efficacious as VKA, with the additional benefits of fewer bleeding complications and drug

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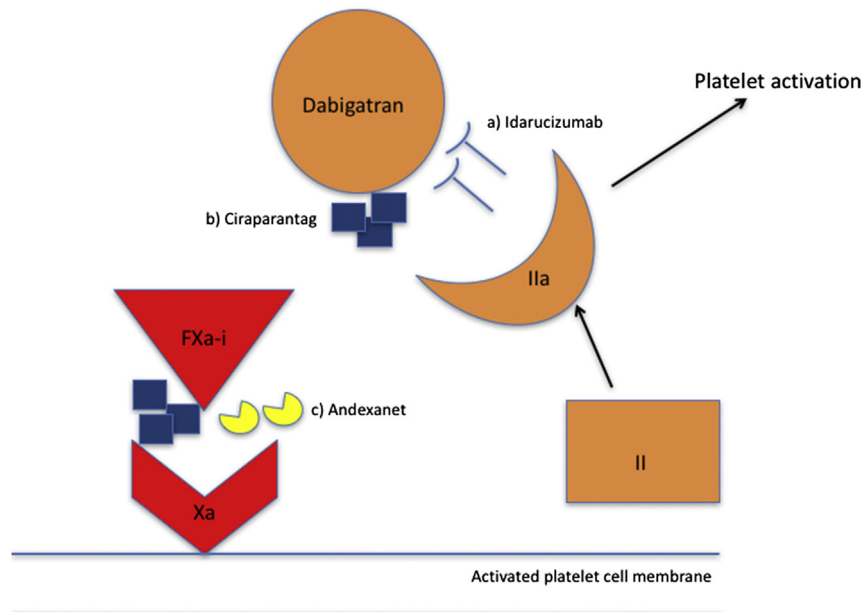


Fig. 1 – Diagrammatic representation of the coagulation cascade and the anticoagulants currently available (red boxes), with their respective points of action. Orange and green boxes represent inactive and active clotting factors, respectively.

interactions, rapid onset of anticoagulation (within 24 h) and predictable pharmacokinetics that obviate the need for dose monitoring.^{1,2}

NOACs are approved for the treatment of venous thromboembolic disease and prevention of embolism in non-valvular atrial fibrillation, though their indications are expanding.² There is currently no consensual guidance regarding bleeding, trauma or perioperative management of patients on NOACs.^{3,4} Consequently, as they can now be expected to be prescribed in 10–20% of treated elderly patients, the management of NOACs remains a matter of concern for surgeons in view of the limited strategies hitherto available to rapidly reverse their effect.⁵

This article summarises the management of patients on NOACs in the context of emergency/trauma surgery or major bleeding, and recent developments of specific antidotes.

Assessing coagulation status and NOACs effect

One of the advantages of NOACs is that, unlike VKA, their predictable pharmacokinetics obviates the need for routine monitoring. Although the absence of tight medical control, which is indeed critical with VKA, could potentially increase risk of bleeding, compelling evidence supports a lower incidence major bleeding associated with NOACs.^{6–9}

When a patient receiving a NOAC requires emergency surgery, it is crucial to ascertain their anticoagulation status prior to considering any reversal strategy. Although there are no specific tests for NOACs, other laboratory tests may help to assess the anticoagulation effect in emergency situations.⁵ For dabigatran, the most sensitive test is thrombin time (TT), which measures the direct activity of thrombin,¹⁰ as prothrombin time (PT) lacks the sensitivity to detect therapeutic levels.^{11,12} All factor Xa inhibitors prolong the PT and a normal

value generally excludes a residual anticoagulation effect, but sensitivity depends on the reagents used and the accuracy of the test improves at higher concentrations.^{11,13}

For both NOAC groups, measurement of INR is unhelpful as this is calibrated exclusively for use with VKA, such as warfarin.¹¹ Although NOACs may lead to higher INR, it should be noted that this increase does not relate to the effectiveness of therapy or provide a linear correlation of concentration and effect that is seen when measuring warfarin levels.^{12,13}

Assays of plasma concentrations of NOACs and anti-Xa activity are the most accurate way to assess the anticoagulation effect. However, they are not widely available in most centres and interpretation relies on extrapolation of data from clinical trials, as there is currently no preclinical or clinical data on which to establish haemostatic safety thresholds.^{5,10,14}

In summary, for patients without a bleeding diathesis, normal PT and activated partial thromboplastin time (aPTT) most likely indicate that the drug concentration is minimal. Therefore, these tests can provide reassurance that it is safe to proceed with emergency surgery without a significant increase in bleeding risk. PT and aPTT can also be used to estimate the time required to reach the safety threshold, but with less accuracy than that based on drug concentration. In addition to basic coagulation tests, it is recommended to check platelet count and fibrinogen level. Point of care thromboelastography provides immediate clotting profile but is not commonly available.

Management of bleeding and emergency/trauma surgery

The management of severe bleeding or emergency surgery is challenging due to the absence of specific antidotes and clear

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