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REVIEW ARTICLE

New oral anticoagulants – a guide for ENT surgeons

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Abstract

Background: New oral anticoagulants have been developed to overcome the perceived disadvantages of more traditional anticoagulants such as heparin and warfarin, and their use amongst ENT patients have been increasing.

Objectives: This review article aims to discuss the mechanism of action of new oral anticoagulants, when they should be used and a protocol for their use, in both the bleeding patient and in the peri-operative setting.

Conclusion: It is important that ENT surgeons are aware of the use of new oral anticoagulants, and have a departmental- and trust-based policy on their use and reversal in bleeding and surgical patients.

Key words: Hemorrhage; Factor Xa Inhibitors; Antithrombins

Introduction

Epistaxis is an extremely common medical condition, which is thought to affect 60 per cent of people at some point in their life.[1] It reportedly constitutes up to 1 per cent of all emergency department admissions, with direct correlations between anticoagulation use and admission to hospital, surgical intervention and a longer length of hospital stay.[2,3] A large number of those presenting with epistaxis to an ENT department are elderly, and using warfarin or low molecular weight heparin in the management of conditions such as atrial fibrillation, stroke, valvular heart disease and thromboembolism. An ageing population and an increase in anticoagulant use will likely lead to an increase in epistaxis rates.[4]

Recently, a number of new oral anticoagulants have been licensed. These drugs have advantages over traditional anticoagulants, which include a rapid onset of action, a shorter half-life and fewer drug interactions.[5] Dabigatran etexilate, apixaban and rivaroxaban have all been licensed by the National Institute for Health and Care Excellence for patients with stroke and non-valvular atrial fibrillation with one or more cardiovascular risk factors, and for thromboprophylaxis during hip and knee surgery.[6–11] Rivaroxaban has also been licensed for the treatment of patients with deep vein thrombosis and pulmonary embolism, and for prevention of their recurrence.[9] With this is mind, as ENT surgeons we are likely to see an increase in new oral anticoagulant use amongst our patients, especially those with epistaxis.

Anticoagulants

Warfarin inhibits the formation of vitamin K and therefore the formation of vitamin K dependent clotting factors. Heparin activates co-factor antithrombin III, which, in turn, deactivates thrombin, and factors Xa, IXa, VIIa, Xia and XIIa. Dabigatran etexilate is a pro-drug that is converted *in vivo* to the direct thrombin inhibitor dabigatran. It is a potent orally active drug that inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. It is mostly excreted through the renal system and should be used in caution with other drugs affecting the kidneys.[12] Apixaban and rivaroxaban are both direct, orally active, highly selective activated factor X inhibitors (Xa inhibitors). There are no specific food interactions with the new oral anticoagulants; however, rivaroxaban should be taken with food as this increases its absorption and bioavailability.[12,13] Figure 1 illustrates the clotting cascade.

Unlike warfarin and to a lesser degree heparin, there is no requirement for regular blood tests or monitoring of the international normalised ratio with new oral anticoagulants. This makes monitoring of the anticoagulant effect during an acute bleed very difficult. It had been stated that an advantage of new oral anticoagulants over traditional anticoagulants is their decreased risk of bleeding; however, the Medicines and Healthcare Products Regulatory Agency denied this in an open letter to all healthcare providers in September 2013.[14]

Managing bleeding

At present, the management of bleeding in patients taking new oral anticoagulants is based on clinical experience and expert opinion, rather than clinical evidence. Currently, no antidote to the new oral anticoagulants exists; however, they have a very short half-life, and their effect fades quickly, 12–24 hours after the last dose.

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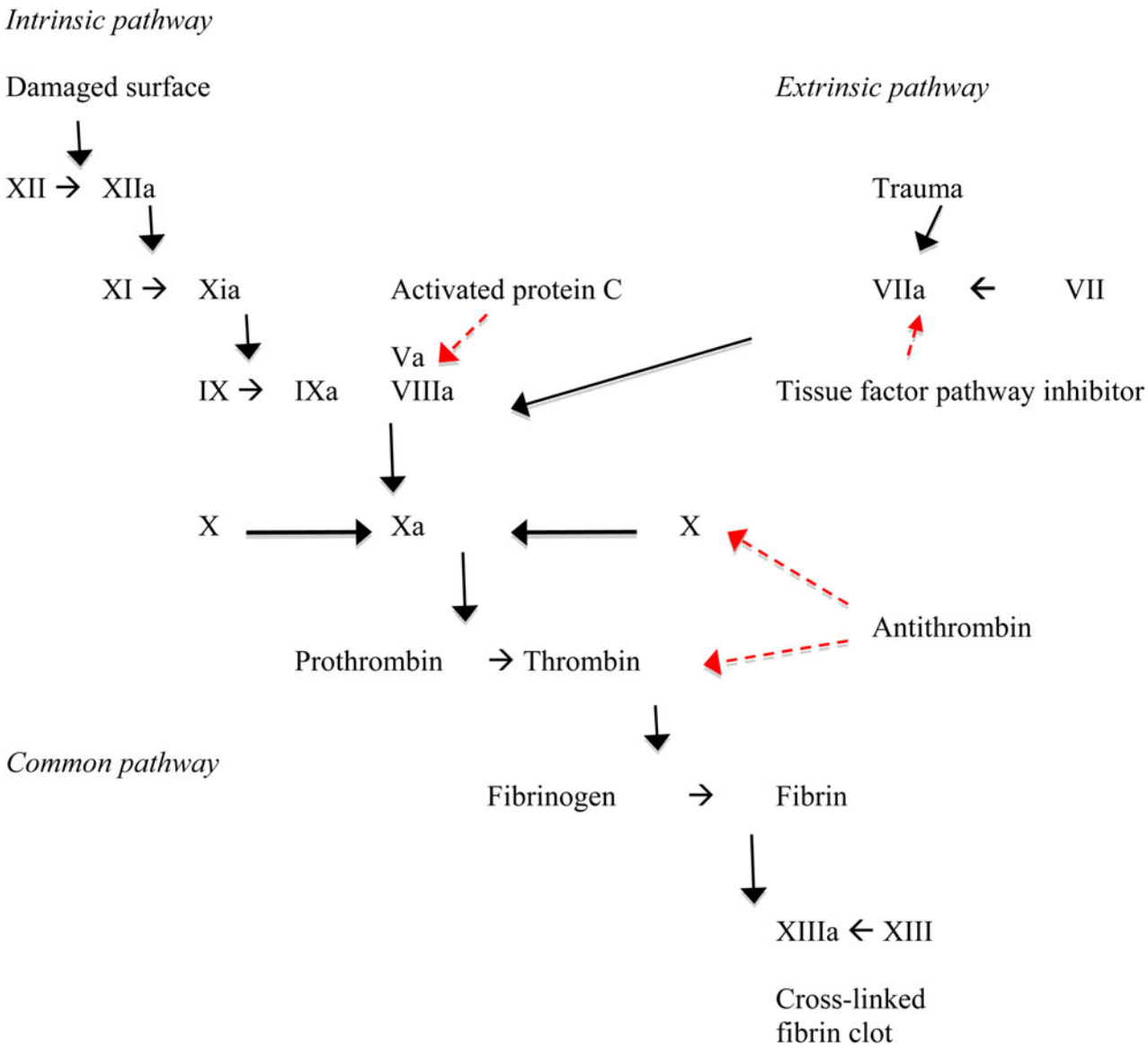

FIG. 1
The clotting cascade.

In the emergency situation, it is vital to know the time of ingestion of the drug and the time of blood sampling. The activated partial prothrombin time can be used for estimating the anticoagulant effect of dabigatran. If the activated partial prothrombin time level at trough (12–24 hours after ingestion) is still two times the upper limit of normal, this poses a significant risk of bleeding. If the patient has taken apixaban or rivaroxaban, then the prothrombin time should be measured. Given the short half-life of these drugs, time is the most important factor in the reversal of the anticoagulant effect. Assessing other factors, such as renal function in the case of dabigatran, and the concomitant use of other antiplatelet drugs, is also essential.

An algorithm for resuscitation and the management of epistaxis in patients taking new oral anticoagulants is shown in Figure 2.[15]

Specialised tests such as those that assess ecarin clotting time and diluted thrombin time can be used to measure the effect of dabigatran. Specialised factor Xa assays can be used in a similar way for apixaban and rivaroxaban. However, these tests are subjective and may not be available locally.

Pre-operative assessment

Cessation of anticoagulants prior to surgery is based on a thorough assessment of the risk of peri-operative bleeding versus thromboembolic events. The type of surgery, duration of surgery, and the patient's renal function and thromboembolic risk factors, should all be assessed. Many ENT surgical procedures are short, and day-case surgery is increasing. Given the relatively short half-life of the new oral anticoagulants, most surgery should be able to be performed safely within 12–24 hours of the last dose. However, given

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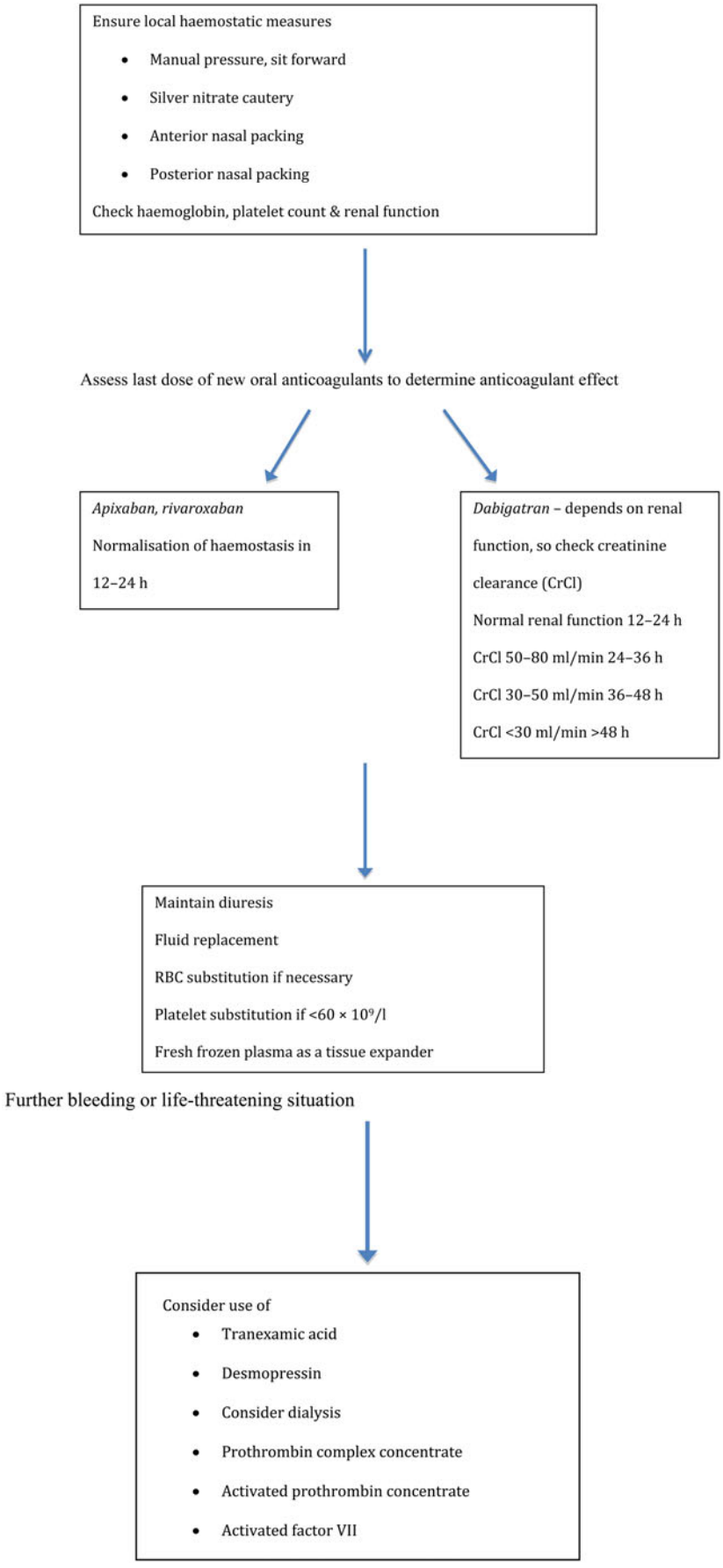

FIG. 2

Non-surgical management of epistaxis in patients taking new oral anticoagulants. Adapted from Heidbuchel *et al.*[15] H = hours; min = minutes; RBC = red blood cell

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TABLE I
GUIDE FOR STOPPING NEW ORAL ANTICOAGULANTS BEFORE ELECTIVE SURGERY DEPENDING ON SURGICAL RISK*

Renal function (CrCl; ml/min)	Dabigatran		Apixaban		Rivaroxaban	
	Low risk	High risk	Low risk	High risk	Low risk	High risk
>80	≥24	≥48	≥24	≥48	≥24	≥48
50–80	≥36	≥72	≥24	≥48	≥24	≥48
30–50	≥48	≥96	≥24	≥48	≥24	≥48
15–30	Not indicated	Not indicated	≥36	≥48	≥36	≥48

Data represent hours pre-operation, unless indicated otherwise. *Adapted from Heidbuchel *et al.*[15] CrCl = creatinine clearance rate; min = minute

the variations in dosing schedules and unpredictability of operating start times, it would be better to have an agreed standardised approach to stopping new oral anticoagulants pre-operatively (Table I).[15]

The benefits and risks of surgery in patients taking any anticoagulation medication should be considered carefully. All surgeons should carry out meticulous haemostasis in every case; however, in patients treated with new oral anticoagulants, extra caution should be taken as currently no antidote is available. One may have a lower threshold for the use of a surgical drain, and, for example, in rhinology cases surgical packing may be considered. It would be sensible to spend longer checking haemostasis at the end of the procedure using manoeuvres such as a head-down tilt of the patient and asking the anaesthetist to perform a Valsalva manoeuvre. Pre-operative control of the patient's blood pressure is essential and surgery should be delayed if this has not been adequately achieved.

Restarting new oral anticoagulants

For procedures with a minor risk of bleeding, new oral anticoagulants can be restarted 6–8 hours after surgery; however, in high risk cases or cases where bleeding may have serious consequences, the reinstating of new oral anticoagulant therapy may need to be delayed to 48–72 hours post-surgery. In procedures with a high risk of bleeding, or procedures in which bleeding has life-threatening consequences or further surgery is required, low molecular weight heparins should be considered as an alternative to new oral anticoagulants as they are reversible. New oral anticoagulants can be commenced at a later date.

Emergency surgery

Little evidence exists as to the management of patients using new oral anticoagulants who require emergency surgery. It would seem sensible to stop the drug and delay surgery 12–24 hours if possible. If not, consult any local guidelines and seek advice from a haematologist. Check the relevant clotting profile (activated partial prothrombin time, prothrombin time or specific tests if available) and renal profile, and ensure the patient has been cross-matched with blood available for transfusion if required. Check that the most senior and experienced team members are available for the procedure. Ensure the team is briefed regarding the patient's anticoagulation status when implementing the pre-operative World Health Organization surgical checklist, and ensure haemostatic agents and equipment (e.g. adrenaline, gauze, ties and clips) are available. The anaesthetist will need to control the patient's blood pressure; close communication between the surgeon and anaesthetist regarding any blood loss intra-operatively is vital.

Conclusion

New oral anticoagulants have been developed to overcome the perceived disadvantages of traditional anticoagulants. As ENT surgeons, we are likely to see an increase in new oral anticoagulant usage amongst our patients. These will include elective surgical admissions as well as patients admitted with acute bleeding such as epistaxis. It is important, therefore, to have departmental and hospital guidelines, developed in communication with local haematologists, regarding anticoagulant use and reversal in bleeding patients that extends to the peri-operative period.

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