Medicines Safety Matters

Newsletter for Prescribers & Community Pharmacists

Health and Social Care Board

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Focus on the non vitamin k antagonist oral anticoagulants - apixaban, dabigatran, edoxaban & rivaroxaban

This issue focuses on incidents involving the non vitamin k antagonist oral anticoagulants (NOACs - also known as direct oral anticoagulants or DOACs). The themes in the NOAC medication incidents are being seen in both primary and secondary care and in some cases, due to the high risk nature of these medicines, have caused serious patient harm. A selection of primary care cases are described and recommendations for actions that could reduce the risk of reoccurrence are summarised on page 4.

1. Unintentional co-prescribing of additional anticoagulants or antiplatelets

NOACs & anticoagulants:
NOACs are contraindicated in combination with other anticoagulants, except in certain circumstances e.g. overlap during switching between agents (see table).

Search for patients prescribed NOACs & check for unintentional co-prescribing of anticoagulants or antiplatelets

NOACs & antiplatelet drugs:
There may be a need to combine an oral anticoagulant with an anti-platelet drug(s) when patients with atrial fibrillation (AF) also develop coronary artery disease (CAD) or acute coronary syndromes (ACS) that may require percutaneous coronary intervention (PCI) or vice versa. In these cases, the initiation of single or dual anti-platelet therapy in combination with a NOAC must be on the recommendation of a specialist ONLY and there should be a clear plan of stepping down to dual or mono therapy[1].

NOAC	Contra-indicated anticoagulants	Caution antiplatelets
• **Apixaban (Eliquis®)** • **Dabigatran (Pradaxa®)** • **Edoxaban (Lixiana®)** • **Rivaroxaban (Xarelto®)**	• **LMWH e.g. enoxaparin, dalteparin** • **Heparin (unless for catheter patency)** • **Other NOACs** • **Warfarin (unless during switch)**	**Not routinely used in combination unless advised by a specialist** • **Aspirin** • **Clopidogrel** • **Dipyridamole** • **Ticagrelor** • **Prasugrel**

Local examples of unintentional co-prescribing:

Patient 1: A 86 year old patient was prescribed enoxaparin 100mg daily for a clotting disorder. The enoxaparin was switched to rivaroxaban. When the patient was admitted to a nursing home their family brought a supply of the injections to the home and they were administered daily in combination with rivaroxaban for 2 weeks. The patient was admitted to hospital with anaemia and bleeding gums. They required a platelet infusion and steroid treatment.

Patient 2: A patient was discharged from hospital on rivaroxaban for the treatment of pulmonary embolus. The discharge note stated 'no other changes to medicines'. The patient was already taking aspirin and continued to take both drugs for almost 1 year.

Patient 3: GP inadvertently commenced rivaroxaban 15mg daily in combination with dipyridamole 200mg m/r. Both medicines were continued for 11 months.

Patient 4: GP stopped rivaroxaban for a 2 week trial of clopidogrel for peripheral vascular disease. After the 2 week period, the rivaroxaban was restarted but the clopidogrel was continued. Both continued for 4 months.

Patient 5: A hospital letter advised treatment for gout and a switch from warfarin to rivaroxaban for a 80 year old patient. The patient did not realize that the rivaroxaban was to replace warfarin and continued to take both anticoagulants. The problem was discovered 6 weeks later when the patient attended the GP. INR was >10.

2. Switching from warfarin to a NOAC

The examples on page 1 illustrate the risks of co-prescribing oral anticoagulants during the process of switching between agents. In another near miss incident, a GP practice planned to switch a patient taking warfarin to dabigatran. The GP issued a prescription for dabigatran and the pharmacist was waiting for the patient to collect their new medicine. It is not clear if robust arrangements were in place at the time to manage the switch e.g. stop the warfarin and monitor the INR before starting the dabigatran, but the patient, carers and pharmacist were not aware of any plan.
At around the same time, the patient became a resident in a care home and on admission, their routine INR was found to be >10. It was fortunate for the patient that they or the home did not co-administer the dabigatran with the warfarin, particularly in the presence of a high INR.

When switching patients from warfarin to a NOAC:

- **Stop warfarin**
- **Monitor INR**
- **INR must be <2 before taking the first dose of apixaban or dabigatran < 2.5 for edoxaban & <3 for rivaroxaban**

(see SPCs)

3. Double dosing errors

In February 2015 we issued advice to highlighting the incidents that involved the continuation of the initial BD dose regimen for rivaroxaban when prescribed for the treatment of DVT/PE[2] .There had been a number of reports where the initial BD dose was continued beyond the 21 day period - in one case for 11 months. (This scenario involving a dose step down is also possible when prescribing apixaban for the same indication). Since then, further incidents have been reported with a similar theme:

Case 1:
A 77 year old patient was discharged from hospital, the letter stated 'rivaroxaban 15mg BD for 21 days followed by 20mg BD'. The correct maintenance dose is 20mg daily.
The letter did not state the proposed duration for anticoagulation. The patient remained on the incorrect BD dose for 1 month before the error was spotted by the GP practice.

Case 2:
A 70 year old patient was discharged from hospital, the letter stated 'rivaroxaban 15mg BD for 21 days then 20mg BD. Lifelong treatment'. The incorrect double dose continued in primary care for 9 months. It appears that the error was noticed during a hospital admission 7 months into treatment as a discharge letter at this stage referred to the correct dose of 20mg daily. However the dose change was not flagged and it was not spotted by the GP practice.

4. Compliance & loss of anticoagulant cover

The anticoagulant effect of NOACs fades rapidly 12–24 hours after the last intake. Strict therapy compliance by the patient is therefore **crucial** for adequate cover for treatment or prevention of clotting. All means to optimize compliance should be considered. These include: considerations on choosing a NOAC with once daily or twice daily intake; repeated patient education, including family members; a clear follow-up schedule; technological aids like medication boxes or smartphone apps.
In NOAC patients in whom low compliance is suspected despite proper education and additional tools, conversion to warfarin could be considered[1].

The anticoagulant effect of NOACs fades rapidly 12–24 hours after the last intake

Case 1:
A patient with previous DVT was started on rivaroxaban in hospital. Following discharge, the rivaroxaban was put on repeats by the GP practice but the patient was not aware that they had started a new anticoagulant and did not order prescriptions for the medicine.
Nine months passed before the omission was spotted during medicines reconciliation in a subsequent hospital admission.

Strict therapy compliance is crucial for adequate cover for treatment or prevention of clotting

5. Increasing patient's anticoagulant awareness

The National Patient Safety Agency (NPSA) advise that for the safe use of anticoagulants[3], it is essential that patients and carers receive adequate verbal and written information about their treatment. This should be provided before starting and when necessary throughout the course of their treatment. The healthcare practitioner who provides this information should record that this information has been supplied. Increasing patient awareness and knowledge of the NOACs supports safe use, compliance and timely management of any untoward events.

Apixaban (Eliquis®)	Dabigatran (Pradaxa®)
Patient information booklets: • Helping to treat deep vein thrombosis and pulmonary embolism & helping prevent recurrence • Helping to prevent stroke caused by atrial fibrillation • Helping prevent blood clots after hip and knee replacement surgery **Counselling guide:** Patient discussion checklist **Patient alert card:** Included inside packs of Eliquis® tablets	**Patient information booklets:** • Stroke prevention in atrial fibrillation • What you should know about Pradaxa to treat DVT & PE and to prevent DVT & PE • What you should know about Pradaxa after your hip or knee replacement operation • Pradaxa patient starter card **Patient alert card:** Included inside packs of Pradaxa® tablets
Available from: BMS/Pfizer Medical Information Tel: 0800 731 1736 Email: medical.information@bms.com Online: www.eliquis.co.uk	**Available from:** Boehringer-Ingelheim Medical Information Tel: 0845 601 7880 Email: medinfo.bra@boehringer-ingelheim.com Online: www.pradaxa.co.uk
Edoxaban (Lixiana®)	**Rivaroxaban (Xarelto®)**
Patient information booklets: • Understanding your treatment for venous thromboembolism • Understanding your treatment for atrial fibrillation **Counselling guide:** • Patient education support guide • Lixiana® mobile phone app to help patient to remember to take their medicine **Patient alert card:** Included inside packs of Lixiana® tablets	**Patient information booklets:** • A patient's guide to stroke & atrial fibrillation • A patient's guide to deep vein thrombosis treatment • A patient's guide to pulmonary embolus treatment • A patient's guide to secondary prevention in acute coronary syndrome (ACS) • A patient's guide for prevention of VTE in hip or knee replacement surgery **Patient alert card:** Included inside packs of Xarelto® and in the patient information booklets
Available from: Daiichi-Sankyo Medical Information Tel: 0800 028 5122 Email: medinfo@daiichi-sankyo.co.uk Online: www.MyAnticoagulant.co.uk (due Oct 2015) Online: www.lixiana.co.uk	**Available from:** Bayer Medical Information Tel: 01635 563 000 Email: medical.information@bayer.co.uk Online: www.xarelto-info.co.uk/

Anticoagulant Alert Card Update

Healthcare staff are familiar with the yellow anticoagulant alert cards issued to patients who are taking warfarin. The alert card is held by the patient and can be shown to healthcare staff during consultations or emergency treatment. The manufacturers of the NOACs provide product specific alert cards (supplied in individual tablet packs) that are to be used in the same way.

Many regions in the UK have also introduced the use of a 'generic' alert card which is used for all NOACs. The intention is to ensure that patients and healthcare staff can quickly and easily recognise that a patient is taking an oral anticoagulant. Some NHS areas have extended use of the yellow oral anticoagulant alert card to NOACs whilst others are developing cards with a similar 'look'. HSCB are planning to use the yellow oral anticoagulant card as a 'generic' warfarin/NOAC alert card in primary care and will be issuing advice in the near future.

Actions - Making NOAC therapy safer in primary care

Patient Review

- Ensure that a full medication review is carried out before a NOAC is commenced
- Ensure that patients are reviewed regularly. EHRA recommends that patients are reviewed one month after initiation and then every 3 months[1]

Dosing

- Be aware of the correct dosage or step down regimens used for each indication. See SPC/BNF.
- Be aware that dosing is highly dependant on renal function and the Cockcroft & Gault formula[4] is used to calculate creatinine clearance (not eGFR).
- Renal function should be monitored regularly[1] and dose adjustments or a switch to warfarin may be necessary depending on the result. See SPC/BNF.
- Ensure that the intended duration of treatment and stop date has been recorded
- Community pharmacists should contact the prescriber directly to query doses of rivaroxaban or apixaban that appear to be prescribed beyond the recommended step down periods

Interactions

- Be aware of the relevant drug interactions and contraindications
- Only prescribe ONE anticoagulant at a time
- Co-prescribing of NOACs and antiplatelet agents should always be checked to establish that the combination has been approved by a specialist. Record interventions on PMR for further reference.

Switching

- Ensure that you refer to a protocol when switching from one oral anticoagulant to another
- Patients must understand that they should not continue the discontinued therapy
- Ensure that discontinued therapy is taken off repeats and moved to 'past drugs'
- Inform carer, community pharmacists or nursing homes as necessary

Supporting Compliance

- Patients must be counselled before they start a NOAC or are switched from one therapy to another. This should be face to face and include the provision of relevant patient information and an explanation of the importance of carrying the patient alert card.
- Ensure that an adequate supply of patient counselling resources is available in your practice
- Consider means to support patient compliance e.g. counselling, choice of agent, use of technical aids and on-going review of tablet re-ordering frequency
- Receptionists and community pharmacists should check re-ordering and dispensing frequencies and highlight any suspected non-compliance with therapy to the GP

[1]European Heart Rhythm Association EHRA Updated Practical Guide on the use of non vitamin k antagonist anticoagulants in patients with non-valvular atrial fibrillation 2015 http://europace.oxfordjournals.org/content/early/2015/08/29/europace.euv309
[2]HSCB letter Incidents involving newer oral anticoagulant dosing - Feb 2015
http://www.medicinesgovernance.hscni.net/primary-care/medicines-safety-advice-letters/
[3]NPSA Actions that can make anticoagulant therapy safer 2007
http://www.nrls.npsa.nhs.uk/resources/?entryid45=59814
[4] Check if the Cockcroft & Gault formula is available in the 'calculators' for renal function on the GP clinical system or use an online calculator e.g. http://www.nuh.nhs.uk/healthcare-professionals/antibiotics/antibiotics-calculators/creatinine-clearance-calculator/