NHS Lothian

Recommendations for Management of Patients on Rivaroxaban (Xarelto®) for Prevention of Stroke and Systemic Embolism; and Treatment of DVT and prevention of recurrent DVT and PE

FOR INDICATIONS, DOSING, USE IN SPECIFIC POPULATIONS AND PATIENT INFORMATION LEAFLET, PLEASE REFER TO THE MANUFACTURER'S SPF AND PRESCRIBING GUIDE.

1.0 Recommendations for conversion to/from other anticoagulants

1.1 Conversion to or from parenteral anticoagulants

Converting from rivaroxaban to parenteral anticoagulants: Give the first dose of parenteral anticoagulant at the time the next rivaroxaban dose would be taken.

Converting from parenteral anticoagulants to rivaroxaban: For patients currently receiving a parenteral anticoagulant, start rivaroxaban 0 -2 hours before the time of the next scheduled administration of the parenteral drug (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral drug (eg. intravenous heparin).

1.2 Conversion to or from warfarin

Converting from Rivaroxaban to warfarin:
There is a potential for inadequate anticoagulation during the transition from rivaroxaban to warfarin. Coninuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.
In patients converting from rivaroxaban to warfarin, the warfarin should be given concurrently until the INR ≥ 2.0. For the first two days of the conversion period, standard initial dosing of warfarin should be used followed by warfarin dosing guided by INR testing. Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Converting from warfarin to rivaroxaban:
Note that INR values will be falsely elevated following the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban and should not be used.

For patients treated for prevention of stroke and systemic embolism, warfarin should be stopped and rivaroxaban should be initiated when the INR is ≤ 3.0.

For patients treated for DVT and prevention of recurrent DVT and PE, warfarin treatment should be stopped and rivaroxaban should be initiated once the INR is ≤ 2.5.

1.3 Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, Rivaroxaban should be stopped at least 24 to 36 hours before the intervention if possible, based on the clinical judgement of the physician, aiming for a normal prothrombin time (PT). If the procedure cannot be delayed there will be an increased risk of bleeding that should be assessed against the urgency of the intervention. Regional anaesthesia will be contra-indicated in such situations. The case can be discussed with the RIE haematology consultant on call (as the haemostasis laboratory can measure serial prothrombin times and Rivaroxaban (anti-Xa) levels if necessary).

Note that in individuals with mild (creatinine clearance 50 -80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15-29ml/min) renal impairment rivaroxaban plasma concentrations are increased 1.4, 1.5 and 1.6-fold respectively with corresponding increases in overall inhibition of anti-factor Xa activity by 1.5, 1.9 and 2.0 respectively, noted by a prolongation of the PT. Rivaroxaban may need to be discontinued earlier in advance of surgery if there is renal impairment; if necessary, pre-operatively the presence of rivaroxaban can be checked by measuring the prothrombin time, and by Rivaroxaban (anti-Xa) levels (desired pre-operative anti-Xa level <25ng/ml).

The timing of re-introduction of rivaroxaban after the invasive procedure will depend on the nature of the surgery or invasive procedure, the bleeding risk associated with the procedure and the thrombosis risk associated with the indication for anticoagulation, as well as the type of anaesthetic given and whether the patient can take oral medications. Note that rivaroxaban is rapidly absorbed with maximum concentrations appearing 2-4 hours after tablet ingestion. That is, the patient will be fully anticoagulated following a single dose of the drug. Note also that the 15mg and 20mg tablet strengths should be taken with food.
Initial thromboprophylaxis will be most simply achieved with low-molecular-weight-heparin (LMWH) at prophylactic doses, as per the LUHD Antithrombotic Guide, and increasing towards therapeutic doses. Once post-operative haemostasis is secure, therapeutic doses of rivaroxaban can be restarted 24 hours after the last dose of LMWH.

Discussion with on call haematology is advised if there is any doubt.

2.1 Management of Bleeding - also refer to algorithm (Appendix 1)

Rivaroxaban has a half-life of 5-13 hours depending upon the age of the patient (half-life is longest in the elderly). There is currently no specific antidote to Rivaroxaban. Management should be individualised according to the severity and location of the haemorrhage.

In the event of haemorrhagic complications:

- Discontinue treatment with rivaroxaban; important to document time of last dose of rivaroxaban.
- Check coagulation screen. If PT is normal then likely LOW level of rivaroxaban anticoagulant effect present.
- Initiate appropriate clinical support e.g. surgical or local haemostasis, transfusion of red cells, volume substitution, inotropic drugs.
- Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used
- Investigate the source of bleeding
- If moderate to severe, or life-threatening bleeding, consult the haematology service.

The following are important points:

- rivaroxaban is eliminated via both renal and faecal routes; therefore maintain adequate diuresis to optimise renal elimination.
- The PT/INR can be used as a qualitative marker of rivaroxaban activity and the haemostasis laboratory can perform rivaroxaban levels following discussion with the on call haematologist.
- Protamine sulphate and vitamin K do not affect the anticoagulant activity of rivaroxaban; there is no experience of the use of antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban.
- The use of activated charcoal may reduce absorption in cases of rivaroxaban overdose (if ingestion < 2hours).
- Due to high plasma protein binding rivaroxaban is not expected to be dialysable.

There is some experimental evidence to support the role of prothrombin complex concentrates eg. beriplex, activated prothrombin complex concentrates eg. FEIBA, or recombinant factor VIIa; however their usefulness in clinical settings has not been evaluated and these alternatives cannot be relied upon.

References

Xarelto 15mg film-coated tablets - Summary of Product Characteristics (SPC) - (eMC).

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PROTOCOL FOR MANAGEMENT OF BLEEDING WITH RIVAROXABAN

rivaroxaban associated bleeding

Initiate standard resuscitation measures; check coag screen ; check FBC, renal function, electrolytes plus calcium

(If PT is normal indicates likely LOW level rivaroxaban effect present).

The haemostasis lab can check rivaroxaban antiXa levels if appropriate: please discuss with on call haematologist (contact via switchboard)

There is no antidote for rivaroxaban; its effect will not be reversed by vitamin K or by fresh frozen plasma

Stop rivaroxaban therapy

(Document time of last dose)

Mild bleeding

Local haemostatic measures

Mechanical compression

Tranexamic acid oral 1g TDS (the intravenous preparation may also be used off-licence topically- please seek advice from on call haematologist)

Delay next dose of rivaroxaban or discontinue treatment as appropriate

Moderate to severe bleeding ♠

Local measures
- eg. Mechanical compression consider surgical/radiological intervention, wound packing

Fluid replacement
- maintain good urine output as rivaroxaban is partly renally eliminated

Blood product transfusion
- consider platelets if levels <70-80x10^9 /L, or if patient on anti-platelet agents; keep >100 x10^9 /L in CNS bleeds

Administration of anti-fibrinolytic agent
- tranexamic acid IV)following initial treatment by intravenous injection, 25-50mg/kg over 24 hours (see BNF)

Oral charcoal if rivaroxaban ingestion <2hours ago

Consult haematology re: off-licence use of prothrombin complex concentrate (PCC)

Life-threatening bleeding §

Implement measures for moderate to severe bleeding and consult with haematology service regarding off-licence use of prothrombin complex concentrate (PCC) (Beriplex 30-50 units/Kg), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa

♠ Moderate to severe bleeding - reduction in Hb≥20g/L, transfusion of > 2 units of red cells or symptomatic bleeding in critical area or organ (eg. Intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding).

§ Life-threatening bleeding - symptomatic intracranial bleed, reduction in Hb ≥50g/L, transfusion of ≥4 units of red cells, hypotension requiring inotropic agents or bleeding requiring surgical intervention.

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