NHS Lothian

Recommendations for Management of Patients on Dabigatran (Pradaxa®) for Stroke Prevention in Atrial Fibrillation

(Please note: Dabigatran is a non-formulary item in NHS Lothian).

FOR INDICATIONS, DOSING AND NEED FOR PATIENT ALERT CARD, PLEASE REFER TO THE MANUFACTURER'S SPF AND PRESCRIBING GUIDE.

1 Conversion to or from parenteral anticoagulants

For patients currently taking dabigatran, wait 12 hours (CrCl ≥30 ml/min) or 24 hours (CrCl <30ml/min) after the last dose of dabigatran before initiating treatment with a parenteral anticoagulant. In patients with an acute coronary syndrome (ACS), or suspected ACS (in whom other anti-platelet agents may be concurrently prescribed), advise initiation of alternative parenteral anticoagulant after at least 24 hours, or call for advice from Haematology.

For patients currently receiving a parenteral anticoagulant, start dabigatran 0 -2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (eg. Intravenous heparin).

2 Conversion to or from warfarin

When converting from dabigatran to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For Cr Cl>50ml/min, start warfarin 3 days before discontinuing dabigatran.
- For Cr Cl 31-50 ml/min, start warfarin 2 days before discontinuing dabigatran.
- For Cr Cl 15-30 ml/min, start warfarin 1 day before discontinuing dabigatran.
- For Cr Cl <15 ml/min, no recommendation can be made - consult with haematology service.

Note: because dabigatran can contribute to an elevated INR, the INR will better reflect warfarin's effect after dabigatran has been stopped for at least 2 days.

When converting patients from warfarin therapy to dabigatran, discontinue warfarin and start dabigatran when the INR is <2.0.

3 Discontinuation before surgery

(For patients at high risk of stroke, advice regarding discontinuation of dabigatran prior to elective surgery can be discussed with haematology or pharmacy).

Renal function CrCl, ml/min	Half-life (hours)	Timing of discontinuation after last dose of dabigatran before surgery	
		High risk of bleeding[a]	Standard risk of bleeding
>80	13 (11-22)	2-4 days before	24 hours before
>50 to ≤80	15 (12-34)	2-4 days before	1-2 days before
>30 to ≤50	18 (13-23)	4 days before	2-3 days before
≤30[b]	27 (22-35)	>5days before	2-5days before

a Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) include but is not limited to cardiac surgery, neurosurgery, abdominal surgery or those involving a major organ. Other procedures such as spinal anaesthesia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age (eg. over 75 years), co-morbidities (eg. major cardiac, respiratory or liver disease), low body weight (eg. Less than 50KG) and concomitant use of antiplatelet therapy.

b Dabigatran etexilate is contra-indicated for use in these patients.

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

There is currently no specific antidote to dabigatran etexilate or dabigatran.

In the event of haemorrhagic complications:

- Discontinue treatment with dabigatran
- Initiate appropriate clinical support eg. 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:

- Dabigatran is primarily eliminated in the urine; therefore maintain adequate diuresis.
- The APTT can be used as a qualitative marker of dabigatran activity; if the APTT is normal then dabigatran is unlikely to be present
- Dabigatran has low protein binding and can be dialysed; it may take 6-8 hours to clear dabigatran this way, and data supporting this approach are limited. Duration of dialysis may be best guided by normalisation of the APTT and/or shortening of the thrombin clotting time to ≤60 seconds.

- The adsorption of dabigatran can be prevented by the administration of activated charcoal within 2 hours of the ingestion of dabigatran.

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

http://fhs.mcmaster.ca/medicine/hematology/anticoag_dabigatran.htm

Pradaxa Prescriber Guide for Stroke Prevention in Atrial Fibrillation, 2011.

Stangier J, Rathgen K, Stähle H et al. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. Clin Pharmacokinet 2010; 49: 259-268.

Van Ryn J, Stangier J, Haertter et al. Dabigatran etexilate - a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010; 103(6) 1116-1127.

Author: Dr Julia A M Anderson, Department of Haematology, Royal Infirmary of Edinburgh.

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PROTOCOL FOR MANAGEMENT OF BLEEDING WITH DABIGATRAN

Dabigatran associated bleeding

Initiate standard resuscitation measures; check coag screen (APTT, thrombin time and fibrinogen assay; check FBC, renal function, electrolytes plus calcium

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

Stop dabigatran therapy

Mild bleeding

Local haemostatic measures

Mechanical compression

Tranexamic acid oral 1g TDS (the intravenous preparation may also be used off-licence topically)

Delay next dose of dabigatran or discontinue treatment as appropriate

Moderate to severe bleeding ♠

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

Fluid replacement
- maintain good urine output as dabigatran excreted renally

Blood product transfusion
- consider platelets if levels <70-80x10^9 /L, or if patient on anti-platelet agents

Administration of anti-fibrinolytic agent
- tranexamic acid IV 15-30mg/kg +/- continuous infusion (1mg/kg/hr)

Oral charcoal if dabigatran 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 activated prothrombin complex concentrate (APCC) or recombinant factor VIIa

Consider haemodialysis if patient stable to do so

♠ 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