DABIGATRAN

TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:

To provide an overview of the mechanism of action, licensed indications, dosing regimens and side-effects of dabigatran.

ABBREVIATIONS:

aPTT	activated partial thromboplastin time
BID	twice daily
CrCl	creatinine clearance
DVT	deep vein thrombosis
INR	international normalized ratio
OD	once daily
PE	pulmonary embolism
PT	prothrombin time
TCT	thrombin clotting time

MECHANISM OF ACTION:

Dabigatran (Pradaxa™) is an oral factor IIa (thrombin) inhibitor. By binding reversibly to the active site of factor IIa, dabigatran attenuates thrombin activity and reduces fibrin formation.

INDICATION:

Dabigatran is currently licensed in Canada for thromboprophylaxis after elective hip or knee replacement surgery (see Thromboprophylaxis: Orthopedic guide), and for stroke prevention in patients with atrial fibrillation who are candidates for oral anticoagulation therapy. The use of dabigatran for the treatment of deep venous thrombosis (DVT), pulmonary embolism (PE) or both is not approved by Health Canada.

DOSING:

a) Thromboprophylaxis: start with 110 mg 1-4 hours after surgery and increase to 220 mg once daily (OD) starting the day after surgery; the 220 mg OD dose is continued for 14 or 30 days after knee or hip replacement, respectively.

b) Stroke prevention in atrial fibrillation: 110 mg twice daily (BID) or 150 mg BID. Patients aged 80 years and older should be treated with a dose of 110 mg BID. There is no recommended dose

adjustment in patients with impaired renal function. Dabigatran is contraindicated in patients with a creatinine clearance (CrCl) < 30 mL/min.

MONITORING:

Routine laboratory monitoring is unnecessary. The prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) do not provide a reliable measure of its activity. To confirm an absent anticoagulant effect, one may use the thrombin clotting time (TCT) which will detect very small amounts of anticoagulant activity. However, the TCT is too sensitive a test for use in routine practice. A dilute TCT test (Hemoclot) can be used to more reliably determine the anticoagulant effect of dabigatran and to detect small amounts of anticoagulant activity, but this assay is not available in all laboratories.

ADVERSE EFFECTS:

A major adverse effect is bleeding; concomitant use of antiplatelet drugs or other anticoagulants increases the bleeding risk. Dabigatran should be avoided in patients with indwelling epidural catheters or with a history of repeated or traumatic spinal punctures, in order to reduce the risk of epidural or spinal hematomas. Dabigatran may be associated with dyspepsia in up to 10% of users; this may improve with use of an anti-ulcer medication such as a proton pump inhibitor, but persistent symptoms warrant additional medical attention.

PERI-PROCEDURAL MANAGEMENT:

See clinical guide Peri-Operative Management of New Oral Anticoagulant Drugs.

SPECIAL CONSIDERATIONS:

Dabigatran crosses the placenta and should not be used in pregnancy or in nursing mothers. Dabigatran is not recommended for use in patients with hepatic dysfunction, particularly those with an associated coagulopathy, due to a lack of clinical data in such patients.

Drugs that inhibit or induce P-glycoprotein should be avoided. Examples include azole antifungals (e.g. ketoconazole), erythromycin, ritanovir and rifampin. Additional potential drug interactions can occur with quinidine and amiodarone. There is no specific antidote for dabigatran.

PEDIATRICS:

There are ongoing studies in children to establish the pharmacokinetics, pharmacodynamics, safety and efficacy of dabigatran in neonates and children. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult

hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

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