Management of bleeding in emergency situations for patients treated with Pradaxa® (dabigatran etexilate)

Updated January 2015
MANAGEMENT OF BLEEDING IN EMERGENCY SITUATIONS FOR PATIENTS TREATED WITH PRADAXA

MEDICAL HISTORY
- Which dose did the patient take?
- When was the last dose taken?
- Comedication increasing the risk of bleeding (such as antiplatelets)?
- Any comorbidities? History of renal impairment?

MANAGEMENT OF PATIENTS TREATED WITH PRADAXA IN CASES OF BLEEDING
- Discontinue Pradaxa
- Investigate the source of bleeding
- Oral charcoal application* (if Pradaxa is ingested <2 h before)
- Maintain adequate hemodynamics and diuresis before initiation of standard treatments:
  - Surgical hemostasis
  - Blood volume replacement (e.g., fresh whole blood or fresh frozen plasma)
  - Application of aprotinin
  - Prothrombin complex concentrates (PCC)* (nonactivated or activated)
  - Platelet concentrates may be considered when thrombocytopenia is present or long-acting antiplatelet drugs (e.g., acetylsalicylic acid or clopidogrel) have been used
- Eliminate Pradaxa via dialysis

MANAGEMENT OF BLEEDING IN PATIENTS TAKING NOVEL ANTICOAGULANTS BASED ON EXPERT OPINION (EUROPEAN HEART RHYTHM ASSOCIATION)1,2

Bleeding while using a NOAC
- Mild bleeding
  - Supportive measures:
    - Mechanical compression
    - Fluid replacement
    - Platelet substitution
  - Consider hemodialysis

- Moderate severe bleeding
  - Supportive measures:
    - Mechanical compression
    - Fluid replacement
    - Platelet substitution
  - Repeat 1x/2x in indicated
  - (rFVIIa* 90 µg/kg no data about additional benefit)

- Life-threatening bleeding
  - Supportive measures:
    - Mechanical compression
    - Fluid replacement
    - Platelet substitution
  - aPCC* 50 IE/kg; max 200 IE/kg/day
  - (rFVIIa* 90 µg/kg no data about additional benefit)
  - Antibiotics (use does not substitute the above mentioned measures; almost no data on NOAC-associated bleeding)

Each treating physician should determine what medical treatment and/or bleeding management measures should be taken on a case by case basis, based on his/her medical experience and judgment.

*Use in NOAC-associated bleeding based on very limited experience in humans.

aPCC: activated prothrombin complex concentrates; PCC: prothrombin complex concentrates; rFVIIa: recombinant Factor VIIa; RBC: red blood cells
PRADAXA PHARMACOLOGY AND EVALUATION OF ANTICOAGULANT ACTIVITY

PRADAXA – PHARMACOLOGICAL DATA³

• Maximum dabigatran plasma concentration 0.5 – 2 h after intake
• 85% renal elimination
• Plasma half-life:

<table>
<thead>
<tr>
<th>Renal function (CrCl mL/min)</th>
<th>Dabigatran half-life (hours)</th>
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</thead>
<tbody>
<tr>
<td>≥80 mL/min</td>
<td>−13</td>
</tr>
<tr>
<td>≥50 – &lt;80 mL/min</td>
<td>−15</td>
</tr>
<tr>
<td>≥30 – &lt;50 mL/min</td>
<td>−18</td>
</tr>
<tr>
<td>&lt;30 mL/min*</td>
<td>27</td>
</tr>
</tbody>
</table>

*Pradaxa is contraindicated in patients with CrCl <30 mL/min

• Protein binding 35%, dabigatran can be dialyzed.¹²

There is limited clinical experience to demonstrate the utility of this approach in clinical studies.

RENAI L FUNCTION MEASUREMENT

The Cockcroft-Gault method is recommended when assessing patients’ creatinine clearance during Pradaxa treatment.²

Cockcroft-Gault formula

For creatinine in mg/dL

$$\frac{(140 \text{ - age (years) \times weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times (0.85 \text{ if female})$$

For creatinine in µmol/L

$$\frac{1.23 \times (140 \text{ - age (years) \times weight (kg)}}{\text{serum creatinine (µmol/L)}} \times (0.85 \text{ if female})$$
Pradaxa does not in general require routine anticoagulant monitoring. However, the quantitative assessment of the drug exposure and the anticoagulant effect may be needed in emergency situations.

- There is a close correlation between the plasma concentration of Pradaxa and the degree of anticoagulant effect.
- The anticoagulant response depends on the time when the blood sample was taken in relation to the last dose administered.
- Serial measurements of anticoagulation tests may provide a guide to the relative clearance of Pradaxa.
- It is important to note that coagulation assays such as the aPTT and ECT may remain elevated despite PCC administration.

**Thrombin Time and Ecarin Clotting Time:** TT and ECT tests assess the anticoagulant activity of direct thrombin inhibitors such as Pradaxa. The most sensitive test is the thrombin time (TT) test. A normal TT measurement indicates no clinically relevant anticoagulant effect of Pradaxa. Due to the lack of standardization, both assays may be prone to substantial interlaboratory variability. Therefore, no reference values for local laboratories can be provided.

**Activated Partial Thromboplastin Time:** The aPTT test provides an approximate indication of the anticoagulation intensity achieved with dabigatran. However, the aPTT test has limited sensitivity and is not suitable for precise quantification of anticoagulant effect, especially at high plasma concentrations of dabigatran. High aPTT values should be interpreted with caution. An aPTT >2 fold the upper limit of normal at trough (when the next dose is due) may be associated with a higher risk of bleeding.

**International Normalized Ratio:** The INR is a specific test for patients treated with vitamin K antagonists. It is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed.

**Recommended measurement of dabigatran plasma concentrations:** For a quantitative measurement of dabigatran plasma concentrations, several dabigatran assays based on diluted thrombin time (dTT) are available. A dTT measure of >200 ng/mL dabigatran plasma concentration prior to the next drug intake may be associated with a higher risk of bleeding. A normal dTT measurement indicates no clinically relevant anticoagulant effect of dabigatran.

### Table: Expected plasma levels of Pradaxa after intake of approved dosages

<table>
<thead>
<tr>
<th>Indication (dose and regimen)</th>
<th>mean Cmax,ss (25th–75th percentile range) (ng/mL)</th>
<th>mean Ctrough,ss (25th–75th percentile range) (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pVTEp (220 mg qd)</td>
<td>71 (35–162)*</td>
<td>22 (13–36)*</td>
</tr>
<tr>
<td>SPAF+VTE (150 mg bid)</td>
<td>175 (117–275)*</td>
<td>91 (61–143)*</td>
</tr>
<tr>
<td>SPAF+VTE (110 mg bid)</td>
<td>126 (85–200)*</td>
<td>65 (43–102)*</td>
</tr>
</tbody>
</table>

*Approximately 2 h after ingestion.

**pVTEp=primary venous thromboembolism prevention; SPAF=stroke prevention in patients with atrial fibrillation; VTE=treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults; qd=once daily; bid=twice daily**
Prescribing information: Pradaxa® (dabigatran etexilate)

Capsules containing 110 mg or 150 mg dabigatran etexilate (as mesilate)

Action: Direct thrombin inhibitor

Indications: Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors (SPAF), such as prior stroke, or transient ischaemic attack; age > 75 years; heart failure (NYHA Class II); diabetes mellitus; hypertension. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (DVT/PE).

Dose and Administration: Renal function should be assessed by calculating CrCl prior to initiation to exclude patients with severe renal impairment (CrCl < 30 mL/min). SPAF: Recommended daily dose 300 mg taken as one 150 mg capsule twice daily. Therapy should be continued long term. DVT/PE: Recommended daily dose 300 mg taken as one 150 mg capsule twice daily following treatment with parenteral anticoagulant for at least 5 days. Duration of treatment should be individualised after careful assessment of the treatment benefit against risk for bleeding. Short duration of therapy (at least three months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. In case of increased risk for major bleeding associated with trauma or surgery, the dose should be reduced if possible and careful monitoring of the patient is recommended. After surgery or injury, the dose should be reduced if possible and careful monitoring of the patient is recommended. After surgery or injury, the dose should be reduced if possible and careful monitoring of the patient is recommended.

References:


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