UAB MEDICINE

Anticoagulant/Thrombolytic Reversal Guidelines

Bold=Formulary Agent

Drug	Elimination Half-life (T ½)	Removal by Hemodialysis (HD)	Reversal Strategies
Direct Factor Xa Inhibitors, Oral			
Apixaban (Eliquis®)	– 12 h (range 7-15) – Prolonged in renal impairment	No	– Activated charcoal: ▪ Apixaban – In healthy subjects administered 2 to 6 h after ingestion of a 20 mg dose reduced AUC by 50% and 27%, respectively ▪ Edoxaban – no information available; could likely be considered if within a few hours of dose ▪ Rivaroxaban –may be considered – Prothrombin Complex Concentrates (PCCs): ▪ If considered, Kcentra® 50 units/kg (maximum dose of 5000 units) ▪ See powerplan titled "Oral Anticoagulant Reversal (Kcentra, PCC, idarucizumab [Praxbind]) – Coagulation Factor Xa, recombinant, inactivated-zhzo (Andexanet alfa; Andexxa®) ▪ Available for reversal of apixaban and rivaroxaban only for patients with intracranial hemorrhage (ICH), meeting criteria for use, and approval by stroke or neurosurgery attending ▪ See Andexanet alfa Guidelines for Use on online UAB Formulary – Anti-Xa lab assay only useful for detecting presence of drug and cannot be used to accurately quantitate the level of drug
Edoxaban (Savaysa®)	– 10-14 h – Prolonged in renal impairment		
Rivaroxaban (Xarelto®)	– Healthy: 5-9 h – Elderly: 11-13 h – Prolonged in renal impairment		
Factor Xa Inhibitors, Parenteral			
Fondaparinux (Arixtra®)	– 17-21 h – Prolonged in renal impairment	Unlikely to be of value	– For uncontrollable bleeding: ▪ Consider rFVIIa (Novoseven®) 90 mcg/kg – Anti-Xa lab assay (specific to fondaparinux)
Direct Thrombin Inhibitors, Oral			
Dabigatran (Pradaxa®)	– 12-17 h – Significantly prolonged in renal impairment	Yes: ~60% Likely rebound upon cessation	– Activated charcoal: ▪ May be considered if 1-2 h after ingestion – Specific reversal agent: ▪ Idarucizumab (Praxbind®) 5 grams IV x 1 (supplied as two separate 2.5 gram vials available from pharmacy) ・ Although data is limited, can consider re-dosing at 5 grams for refractory bleeding – Consider HD for patients with refractory bleeding or especially in those with impaired renal function – Thrombin time can be used to assess presence of drug in circulation
Direct Thrombin Inhibitors, Parenteral			
Bivalirudin (Angiomax®)	– 25 min – Significantly prolonged in renal impairment	Yes: 25%; HD generally not practical	– Turn off the infusion – aPTT lab assay is used to assess the degree of anticoagulation
Argatroban	– 30-51 min – Prolonged in hepatic impairment	Yes: 20%; HD generally not practical	

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<table>
<tr><th>Drug</th><th>Elimination Half-life (T ½)</th><th>Removal by Hemodialysis (HD)</th><th>Reversal Strategies</th></tr>
<tr><td colspan="4">Heparins/Low Molecular Weight Heparins (LMWH)</td></tr>
<tr><td rowspan="4">Enoxaparin (Lovenox®)</td><td rowspan="4">– 4.5-7 h
– Prolonged in renal impairment</td><td rowspan="4">Unlikely to be of value</td><td colspan="3">– Protamine partially neutralizes anti-Xa activity (~60%)</td></tr>
<tr><td>Time since last dose</td><td colspan="2">Dose of protamine for each 1 mg of enoxaparin or 100 units of dalteparin</td></tr>
<tr><td>≤ 8 h</td><td>1 mg</td><td rowspan="3">Maximum of 50 mg in 10 min period</td></tr>
<tr><td>8-12 h</td><td>0.5 mg</td></tr>
<tr><td>Dalteparin (Fragmin®)</td><td>– 3-5 h
– Prolonged in renal impairment</td><td></td><td>> 12 h</td><td>Not likely to be useful</td><td></td></tr>
<tr><td rowspan="5">Unfractionated Heparin</td><td rowspan="5">– ~ 1.5 h
(T ½ of the anticoagulant effect)</td><td rowspan="5">No</td><td colspan="3">– Protamine provides rapid reversal of anticoagulant effects (measured by anti-Xa activity)
▪ Only heparin given in preceding several hours needs to be considered when calculating dose of protamine (e.g. the previous 2-2.5 h if given as continuous infusion)</td></tr>
<tr><td>Time since last dose</td><td colspan="2">Dose of protamine for each 100 units of heparin</td></tr>
<tr><td>Immediate</td><td>1 mg</td><td rowspan="3">Maximum of 50 mg in a 10 min period</td></tr>
<tr><td>30 minutes – 2 hours</td><td>0.5 mg</td></tr>
<tr><td>> 2 hours</td><td>0.25 mg</td></tr>
<tr><td colspan="4">Vitamin K Antagonists</td></tr>
<tr><td rowspan="6">Warfarin (Coumadin®)</td><td rowspan="6">– Single dose terminal: ~1 week
– Effective T ½ = 20-60 h</td><td rowspan="6">No</td><td colspan="3">Based on 2012 Chest Guidelines:
– Any major/life-threatening bleeding
▪ 4-factor PCC (Kcentra) AND Vitamin K 10 mg by slow IV injection (mixed in minimum 50 mL and given over at a rate not exceeding 1 mg/min [i.e. 10 mg over 10 min])</td></tr>
<tr><td>Pre-treatment INR*</td><td colspan="2">Kcentra Dose</td></tr>
<tr><td>2 to < 4</td><td colspan="2">25 units/kg (Maximum 2500 units)</td></tr>
<tr><td>4 – 6</td><td colspan="2">35 units/kg (Maximum 3500 units)</td></tr>
<tr><td>>6</td><td colspan="2">50 units/kg (Maximum 5000 units)</td></tr>
<tr><td colspan="3">– INR between 4.5 and 10 and no evidence of bleeding – suggest <u>against</u> the routine use of vitamin K
– INR > 10 and no evidence of bleeding – suggest oral vitamin K be administered (speak to your pharmacist about dosing)
Alternative recommendations:
– INR > 4.5 and no evidence of bleeding: Vitamin K PO 1 – 2.5 mg
– Minor bleeding: Vitamin K PO 2.5 – 5 mg (with possible repeat dose at 24h)</td></tr>
<tr><td colspan="4">Thrombolytics</td></tr>
<tr><td>Alteplase</td><td>– Initial: ~5 min
– Following 90 min infusion: 27-46 min</td><td rowspan="2">No</td><td colspan="3" rowspan="2">– Discontinue thrombolytic agent
– Thrombolytic-associated symptomatic intracranial hemorrhage
▪ Consider cryoprecipitate (10 units initial dose; 1 bag = 5 units) to a goal fibrinogen >150 mg/dL in patients who have received thrombolytic agent in the previous 24 hours
▪ If cryoprecipitate is contraindicated, consider aminocaproic acid 4-5 g IV over 1 hour or tranexamic acid 10-15 mg/kg IV over 20 mins
▪ Consider platelet transfusion for platelet counts < 100k</td></tr>
<tr><td>Tenecteplase</td><td>– Initial: 20-24 min
– Terminal: 115 min</td></tr>
</table>

*For emergent reversal of an INR < 2, a typical dose of 15 units/kg may be used but is up to the discretion of Transfusion Medicine Consult Resident

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Andexanet Dosing/Criteria

P&T-Approved Criteria

Restricted to approval by stroke or neurosurgery attending for patients with potentially life-threatening intracranial hemorrhage (ICH) presenting within 48 hours of symptom onset AND the following four criteria are met:

- Last dose of apixaban or rivaroxaban within 18 hours of presentation (reasonable effort to confirm timing of last dose)
- ICH volume ≤ 60 mL
- No administration of prothrombin complex concentrates (PCC) within previous 48 hours
- No concurrent evidence of life-threatening thrombotic complications

Andexanet alfa will be restricted to one dose (no re-dosing or extension of infusion).

Dosing and Administration

Dosing

<table>
<tr><th rowspan="2">Last Dose</th><th colspan="2">Time since last dose</th></tr>
<tr><th>< 8 h or unknown</th><th>≥ 8 h</th></tr>
<tr><td>• Apixaban > 5 mg
• Rivaroxaban > 10 mg
• Unknown dose</td><td>“High Dose”
Bolus: 800 mg
Infusion: 8 mg/min up to 120 min</td><td rowspan="2">“Low Dose”
Bolus: 400 mg
Infusion: 4 mg/min for up to 120 min</td></tr>
<tr><td>• Apixaban ≤ 5 mg
• Rivaroxaban ≤ 10 mg</td><td>“Low Dose”
Bolus: 400 mg
Infusion 4 mg/min up to 120 min</td></tr>
</table>

In the ANNEXA-4 study, 208 patients (84%) received the “Low Dose”