Warfarin, INRs and Reversal

4th most prescribed cardiovascular agent; 11th most commonly prescribed drug in US

Mechanism: √ Interferes with Vitamin K dependent clotting factors in liver; affects factor II, VII, IX, X, protein C and S (inhibits enzyme, which convert Vitamin K from inactive \(\rightarrow\) active form, which is a cofactor in the carboxylation reaction)

Pharmacokinetics: √ 99% bound to albumin; only non-protein bound fraction is active
√ Metabolized in liver
√ Half life\(\rightarrow\)warfarin \~40hrs, duration of effect is 2-5days

Pharmacodynamics: √ Follow INR (PT ratio using a WHO reference to standardize values)
√ Anticoagulant effect\(\rightarrow\)does not affect the body’s physiologic ability to halt clot expansion or form new thromboses.
√ INR may change in 24hrs, because of Factor VII (half-life 6 hrs)
√ Protein C (half-life 8hrs)\(\rightarrow\)may potentiate a hypercoagulable state during the first 36hrs, because of rapid an severe reduction of this factor.
√ Antithrombotic effect\(\rightarrow\)inability to expand or form clots not present until about 5days because of Factor II (half-life 50 hrs).

Therapeutic Levels:
- Atrial fibrillation goal INR 2-3
- Cardioversion goal INR 2-3
- Deep Vein Thrombosis goal INR 2-3
- Pulmonary Embolism goal INR 2-3
- Cardioembolic Cerebral event goal INR 2-3
- Mechanical Valve goal INR 2.5-3.5
- Antiphospholipid Ab goal INR 2-3 (2.5-3.5)

Risks:
√ Major Bleeding 0.9-2.7% annually
√ Fatal Bleeding 0.07-0.7% annually
√ Risk Factors for bleeding\(\rightarrow\) age>65, age>75 with a fib, h/o GIB, comorbid states (HTN, CRI, CVD), bleeding disorder, INR instability, use of NSAIDs
√ Bleeding Risk Index\(\rightarrow\)age>65, h/o CVA, h/o GIB, Hct <30, recent MI, Cr >1.5mg/dL, DM

Major bleeds @48mos: low risk(0 risk factors)\(\rightarrow\)3%
moderate(1-2 risk factors)\(\rightarrow\)12%
high (>3risk factors)\(\rightarrow\)53%

Elevated INRs:

<table>
<thead>
<tr>
<th>INR</th>
<th>No bleeding</th>
<th>Hold 1dose and adjust weekly dose by 10-20%</th>
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<tbody>
<tr>
<td>&lt;5</td>
<td></td>
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<tr>
<td>5-9</td>
<td></td>
<td>Hold 1-2 doses and adjust weekly dose by 10-20% and/or oral Vit K 1-2.5mg (&lt;5mg)</td>
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<tr>
<td>&gt;9</td>
<td></td>
<td>Hold 1-2 doses and adjust weekly dose by 10-20% and/or oral Vit K 3-5mg (5-10mg)</td>
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<tr>
<td>&gt;20</td>
<td>Or bleeding at above levels</td>
<td>Hold warfarin, Vit K IV 10mg over 20-60min, FFP (15ml/kg, 1unit =220ml) pm, Prothrombin Complex Concentrate (50units/kg)pm, recombinant factor VII pm</td>
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</tbody>
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NOTE: retrospective review of 633 pts with INR 6-10, dose held x2days and INR rechecked. 34% still INR >4; 12% INR <2

Vitamin K:
√ Made by gut flora, absorbed in duodenum
√ Onset of action\(\rightarrow\) PO in 6-12 hrs; IV 1-2 hrs; avoid SQ if possible; never IM
√ PT normalizes in 12-14 hrs following adequate doses

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