Things That Make Your INR Go Hmmm: Pearls From An Emergency Pharmacist

Dawn Dalen, BSc, ACPR, PharmD
Clinical Practice Leader – Pharmacy – Central Okanagan
Clinical Pharmacy Specialist – Emergency Medicine
Interior Health Authority
Clinical Assistant Professor, UBC Faculty of Pharmaceutical Sciences
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Objectives
- To gain an approach for the patient with an INR over 10, without significant bleeding.
- To understand drug interactions with the newer oral anticoagulants.
- To identify a system for approaching warfarin therapy, while patients are receiving antimicrobials.

Scenario One
- 71 yo female admitted with 8 day hx diarrhea/abdo pain
- PMH: PE, atrial fibrillation, diverticulitis
- MPTA: warfarin 2.5 mg daily
- OE: VSS, afebrile
- 10/10 LLQ pain, normal BS, soft, non-distended no guarding, no rebound
- WBC 12.8; neut 10.4; Hb 132; INR >10
- CT: diverticulitis sigmoid colon
- Given Vit K 10 mg SC

Background
- Approach depends on risk of bleeding, active bleeding, indication and INR
- Risk factors for major bleeding
  - History of major bleed, stroke, anemia, RF, HTN, age
  - Intensity of anticoagulation
  - Annual rate of major bleeding 1.3%
  - < 4% will have major bleed with INR > 6
- Goal of Vit K is to lower INR just enough
- Onset: Oral 6 h, IV 1 h
- Peak Effect: Oral 24-48 h, IV 12-14 h
- Give IV over 30 min to decrease risk anaphylaxis

Literature Search
- Databases
  - Medline (1950), EMBASE (1980), IPA (1970), Cochrane Databases (CDSR, ACP, DARE, CCTR, CMR) to present
- Search terms
  - Warfarin, supratherapeutic INR (limit to studies looking at INR >10), Vitamin K
- Results
  - 1 Observational trial
  - Chest 2008 Guidelines
  - Thrombosis Interest Group of Canada
Gunther, et al

Objective
Observational trial to determine if low dose Vitamin K alters bleeding in those with INR > 10

Primary outcome
Major Bleeding at day 3

Intervention
(both warfarin held)
Same day return: Vitamin K 2 mg po (n=51)
Could not return: No Vitamin K (n=25)

Inclusion
Outpatient with INR >10 and no bleeding

Exclusion
Bleeding, possible bleeding, prosthetic valve

Table 1  Baseline characteristics of all patients

<table>
<thead>
<tr>
<th>Mean age (age range), years</th>
<th>49 (16-83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>65%</td>
</tr>
</tbody>
</table>

Indications for warfarin—number of patients:
- Atrial fibrillation: 20
- Prosthetic valve: 19
- Venous thromboembolic disease: 30
- Other: 16

Table 2  Incidence of adverse clinical events

<table>
<thead>
<tr>
<th>Adverse clinical events</th>
<th>Warfarin withdrawal alone (n=23)</th>
<th>Warfarin withdrawal plus vitamin K (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding episodes</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>at presentation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>during management</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Difficultly with re-anticoagulation</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- No Vitamin K
  - 2 minor - epistaxis
  - 1 hematemesis – admitted
- Vitamin K
  - 1 minor - gum bleeding
  - 11.1% had INR > 5 at day 3

46.7% had INR > 5 at day 3

Vitamin K
- 1 minor - gum bleeding
- 11.1% had INR > 5 at day 3

INR more than therapeutic range but < 5.0; no significant bleeding

Lessen dose or omit dose; monitor more frequently and resume at lowest dose when INR therapeutic; if only minimally above therapeutic range, gradual reduction may be required (Grade IC).

INR ≥ 5.0, but < 9.0; no significant bleeding

- INR ≥ 5.0, but < 9.0; no significant bleeding
- INR ≥ 5.0, but < 9.0; no significant bleeding
Our Patient

- Investigate the cause
- Hold warfarin
- Vitamin K 2.5 – 5 mg po
- INR in 48 hours, unless bleeding occurs
- May require bridging with UFH drip
- Piperacillin/tazobactam 3.375 g IV q6h

Scenario Two

- 72 yo male with R visual field defect at home
- PMH: stroke, afib, seizures
- HPI:
  - Seizure 3 weeks prior
  - Carbamazepine level 13 (400 mg am & 200 mg pm)
  - Phenytoin 300 mg bid added
  - Dabigatran 150 mg bid two weeks prior as difficulty with INR
  - Also taking esomeprazole 20 mg daily
- VSS, vision normal, no focal weakness
- Labs: Ptt 26, INR 1.0
- CT: old L parietal & old cerebellar infarct
**Background - Dabigatran**

- Competitive, reversible, thrombin inhibitor
- May elevate PTT & PT
- Kinetics:
  - Absorbed in low gastric pH
  - Hydrolyzed by liver to active form
  - Glucuronidation in liver & 80% elimination via kidney
  - $T_{1/2}$ = 12-17 hours
    - Elderly (dose reduction if > 75 years)
    - Renal failure (not if CrCl < 30)
- Dose:
  - Afib – 150 mg po bid
  - Ortho – 220 mg po daily for 10 days (TNK) or 28-35 days (THR)

**Background - Rivaroxaban**

- Competitive inhibitor of factor Xa
- May elevate PTT & PT – not sensitive
- Kinetics:
  - Metabolized in liver via CYP 3A4, 3A5, & 2J2
  - 33% eliminated in urine unchanged
  - $T_{1/2}$ = 5-9 hours
    - Prolonged in elderly
    - Not recommended with CrCl < 30 ml/min
- Dose:
  - Ortho – 10 mg po daily for 14 days (TKR) or 35 days (THR)

**Literature Search**

- Databases
  - Medline (1950), EMBASE (1980), IPA (1970), Cochrane Databases (CDSR, ACP, DARE, CCTR, CMR) to present
- Search terms
  - Rivaroxaban, Xarelto, Dabigatran, Pradax, Drug Interaction
- Results
  - No peer reviewed publications
  - Monograph
  - Lexi-Drugs
  - Health Canada Adverse Drug Reaction Database

**Dabigatran**

- Increased Dabigatran (↑53-240%)
- P-glycoprotein inhibitors
  - Amiodarone, azoles, carvedilol, clarithromycin, cyclosporine, dipyridamole, dronedarone, erythromycin, grapefruit juice, propafenone, quinine, tacrolimus, tamoxifen, verapamil
- Increased bleeding with Dabigatran
- Other anticoagulants, antiplatelets, NSAIDs, herbal products

**Rivaroxaban**

- Increased Rivaroxaban
  - CYP 3A4 and p-glycoprotein inhibitors - avoid
    - Amiodarone, azoles, clarithromycin, cyclosporine, dronedarone, erythromycin, grapefruit juice, isoniazid, quinine, tacrolimus, verapamil, voriconazole
- Increased bleeding with Rivaroxaban
  - Other anticoagulants, antiplatelets, NSAIDs, herbal products

**Dabigatran**

- Decreased Absorption (↓ 40%)
- Antacids, H2RA, PPI
- Decreased Dabigatran (↓ 66%)
- P-glycoprotein inducers
  - Carbamazepine, dexamethasone, prazosin, rifampin, St. John’s wort, trazodone
Rivaroxaban

- Decreased Rivaroxaban
  - CYP 3A4 inducers (over 50% ↓)
    - Carbamazepine, dexamethasone, oxcarbazepine, phenytoin, rifampin

Health Canada

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Reports</td>
<td>28</td>
<td>123</td>
</tr>
<tr>
<td>Related to Thrombosis</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>Related to Bleeding</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Potential Interaction</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Interaction Details</td>
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<td></td>
</tr>
<tr>
<td>1 Bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- on other anticoagulant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- on PPI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- on atorvastatin</td>
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Our Patient

- Was on a PPI & carbamazepine
  - Both decrease dabigatran
- Likely cause?
  - Ptt & INR normal
- Plan:
  - Restart warfarin
  - Carbamazepine 400 mg bid & d/c phenytoin
- Newer is not always better
  - Limited safety information
  - No reversal agents

Scenario Three

- 82 yo female with CC weak, confused
- HPI:
  - Urgency, frequency 4d ago - GP started septra
  - Now feeling unwell, confused
- PMH: afib, HTN, dementia
- MPTA:
  - Warfarin 2 mg po daily
  - Bisoprolol 2.5 mg po daily
- OE: BP 100/60; HR 96; temp 38.0
- Labs: WBC 12.0; neut 10.2; INR 4.5
- Urinalysis: leukocytes & nitrite positive

Background

- Most common interaction
- Mechanism:
  - Inhibition of CYP 2C9, 1A2 or 3A4
  - Elimination of Vit K producing bacteria in GI tract
  - Displacement of VKA bound to protein
- Risk GI bleeding
  - Septra - OR 1.68
  - Fluconazole - OR 2.09
- Effect on INR
  - 1-3 days clarithromycin, norfloxacin, trimethoprim
  - >3 days amoxicillin, doxycycline, septra

Table 3. Clinically Significant Interactions With Warfarin by Level of Causation and Drug Group

<table>
<thead>
<tr>
<th>Level of Causation</th>
<th>Anticoagulants</th>
<th>II (Possible)</th>
<th>III (Possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Highly probable)</td>
<td>Add-ons:</td>
<td>Amoxicillin/metronidazole</td>
<td>Anadrol,raloxifene, lipitor</td>
</tr>
<tr>
<td></td>
<td>Antithrombin71</td>
<td>Clarithromycin</td>
<td>Claramin,sertraline</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>Enalapril</td>
<td>Enalapril,sertraline</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>Lisinopril</td>
<td>Lisinopril,sertraline</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>Nitrates</td>
<td>Nitrates,sertraline</td>
</tr>
<tr>
<td></td>
<td>Ticlopidine</td>
<td>Tiapride</td>
<td>Tiapride,sertraline</td>
</tr>
</tbody>
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Literature Search

- Databases
  - Medline (1950), EMBASE (1980), IPA (1970), Cochrane Databases (CDSR, ACP, DARE, CCTR, CMR) to present

- Search terms
  - Warfarin, supratherapeutic INR, antibiotic, drug interaction

- Results
  - 1 Observational trial

Ahmed, et al

- Objective
  - Determine role of dose reduction when antibiotics are prescribed

- Primary outcome
  - INR value within 7 days

- Intervention
  - 10-20% dose reduction in warfarin dose (n=18) vs. no dose adjustment (n=22)

- Inclusion
  - Patients receiving septran or levofloxacin (7 days min.)
  - On antibiotic for <48 hours at study enrollment
  - Stable INR x 6 weeks

- Exclusion
  - No other antibiotic within 4 weeks


Table 1 Baseline patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Dose-reduction group (n=18)</th>
<th>Control group (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70 ± 30</td>
<td>66 ± 19</td>
<td>0.64</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>80 ± 20</td>
<td>75 ± 15</td>
<td>0.58</td>
</tr>
<tr>
<td>Target INR range</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (5)</td>
<td>2 (9)</td>
<td></td>
</tr>
</tbody>
</table>


Fig. 1 Mean pre-antibiotic (empty bars) and post-antibiotic (black bars) INR values for the warfarin DR and control groups, for TMP-SMX- and levofloxacin-treated patients. *P < 0.02 vs. corresponding pre-antibiotic INR

Our Patient

- Hold at least one dose of warfarin
  - Repeat INR in 24 h
  - Once INR in therapeutic range restart at reduced dose
  - No Vit K necessary – no active bleeding
  - Ceftriaxone 1 g IV daily until C&S back
  - Next time
    - 10-20% empiric dose reduction for warfarin?


- Septara
  - No sub-therapeutic INR in either group
- Levofloxacin
  - 4 sub-therapeutic INR (1.8-1.9) in DR group

References