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

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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

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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 (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

Thromb Res 2004;113:205-9.

Gunther,et al

Table 1 Baseline characteristics of all patients

Mean age (age range), years	49 (16–83)
Women	65%
Indications for warfarin– number of patients:	
Atrial fibrillation	20
Prosthetic valve	19
Venous thromboembolic disease	30
Other	16

Thromb Res 2004;113:205-9.

Gunther,et al

Table 2 Incidence of adverse clinical events

Adverse clinical events	Warfarin withdrawal alone (*n* = 23)	Warfarin withdrawal plus vitamin K (*n* = 51)
Bleeding episodes		
at presentation	0	1
during management	3	0
Thrombosis	0	0
Difficulty with re-anticoagulation	0	0

- No Vitamin K
  - 2 minor - epistaxis
  - 1 hematemesis – admitted
  - 46.7% had INR > 5 at day 3
- Vitamin K
  - 1 minor - gum bleeding
  - 11.1% had INR > 5 at day 3

Thromb Res 2004;113:205-9.

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Table 5—*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs (Section 2.4)**

Condition†	Intervention
INR more than therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required **(Grade 1C)**.
INR ≥ 5.0, but < 9.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), particularly if at increased risk of bleeding **(Grade 1C)**. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤ 5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg po) can be given **(Grade 2C)**.
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h **(Grade 1B)**. Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
Serious bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with FFP, PCC, or rVIIa, depending on the urgency of the situation; vitamin K can be repeated q12h **(Grade 1C)**.
Life-threatening bleeding	Hold warfarin therapy and give FFP, PCC, or rVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR **(Grade 1C)**.
Administration of vitamin K	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously **(Grade 1A)**.

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Table 5—*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs (Section 2.4)**

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

Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required **(Grade 1C)**.

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Table 5—*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs (Section 2.4)**

INR ≥ 5.0, but < 9.0; no significant bleeding

Omit next one or two doses, monitor more frequently, and resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), particularly if at increased risk of bleeding **(Grade 1C)**. If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤ 5 mg po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg po) can be given **(Grade 2C)**.

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Table 5—*Recommendations for Managing Elevated INRs or Bleeding in Patients Receiving VKAs (Section 2.4)**

Condition†	Intervention
INR more than therapeutic range but < 5.0, no	Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if omit minimally above therapeutic range, no dose reduction may be required **(Grade 1C)**.
INR ≥ 9.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h **(Grade 1B)**. Monitor more frequently and use additional vitamin K if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.
	In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously **(Grade 1A)**.

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TIGC

- INR > 10 without bleeding
  - Correct cause
  - Withhold at least 2 doses and check INR 24 hrs
  - Consider restart at lower dose
  - Vitamin K 2.5 – 5 mg po
  - Can be treated as outpatient if no bleeding
- Based on consensus due to lack of evidence

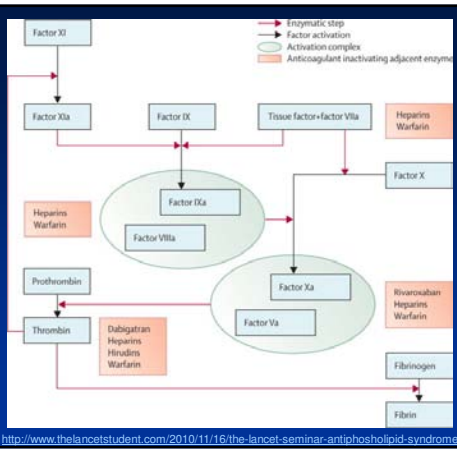
http://www.tigc.org/clinical-guides/Managing-warfarin-associated-coagulopathy.aspx

Our Patient

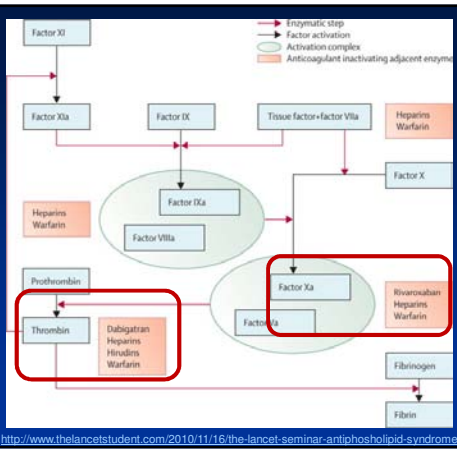
- Investigate the cause
- Hold warfarin
- Vitamin K 2.5 – 5 mg po
- INR in 48 hours, unless bleeding occurs
- May require bridging with UFH drip
- Piperacillin/tazobactam 3.375 g IV q6h

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



http://www.thelancetstudent.com/2010/11/16/the-lancet-seminar-antiphospholipid-syndrome/



http://www.thelancetstudent.com/2010/11/16/the-lancet-seminar-antiphospholipid-syndrome/

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 ½ = 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)

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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 ½ = 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)

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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, progesterone, propranolol, quinine, tacrolimus, tamoxifen, verapamil
- Increased bleeding with Dabigatran
  - Other anticoagulants, antiplatelets, NSAIDs, herbal products

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Dabigatran

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

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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

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Rivaroxaban

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

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Health Canada

	Dabigatran	Rivaroxaban
Number of Reports	28	123
Related to Thrombosis	10	44
Related to Bleeding	7	37
Potential Interaction	**4**	**13**
Interaction Details	**1 Bleed** -on other anticoagulant **1 Thrombosis** -on PPI **2 Hepatitis** -on atorvastatin	**13 Bleed** -on other anticoagulant/antiplatelet -1 on amiodarone -1 on simvastatin

http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php

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

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Clin Pharmacol Ther 2008;84(5):581-88.
Thromb Haemost 2002;88:705-10.

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

Level of Causation	Anti-infectives
I (Highly probable)	Ciprofloxacin[16] Cotrimoxazole[77] Erythromycin[78] Fluconazole[79] Isoniazid (600 mg/d)[80] Metronidazole[81] Miconazole oral gel[82] Miconazole vaginal suppositories[75] Voriconazole[83]
II (Probable)	Amoxicillin/clavulanate[123] Azithromycin[124] Clarithromycin[126] Itraconazole[127] Levofloxacin[130] Ritonavir[60] Tetracycline[150,151]
III (Possible)	Amoxicillin[11] Amoxicillin/tranexamic rinse[176] Chloramphenicol[178] Gatifloxacin[186] Miconazole topical gel[193] Nalidixic acid[194] Norfloxacin[195] Ofloxacin[197] Saquinavir[201] Terbinafine[59]
IV (Highly improbable)	Cefamandole[214] Cefazolin[214] Sulfisoxazole[222]

Holbrook et al. Arch Int Med 2005;165:1095-1106.

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 septra 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

Ahmed , et al. J Thromb Thrombolysis 2008;26(1):44-8.

Table 1 Baseline patient characteristics

Patient characteristics	Dose-reduction group ($n = 18$)	Control group ($n = 22$)	*P*-value
Demographics			
Male	7 (39)	4 (18)	0.17
Female	11 (61)	18 (82)	0.17
Age (years)	70 ± 10	66 ± 19	0.64
Weekly warfarin dose (mg)	35 ± 18	35 ± 16	0.78
Target INR range			
2–3	17 (94)	20 (91)	0.613
Other	1 (5)	2 (9)	
Anticoagulation diagnosis			
Atrial fibrillation	7 (39)	6 (27)	0.44
DVT/PE	4 (22)	9 (41)	0.21
Prosthetic valve	3 (17)	3 (14)	1.00
Hypercoagulable state	4 (22)	2 (9)	0.38
Other	0 (0)	2 (9)	0.49
Antibiotic			
TMP-SMX	8 (44)	9 (41)	0.80
Levofloxacin	10 (56)	13 (59)	0.99

Numbers in parentheses represent % of total patients for each group

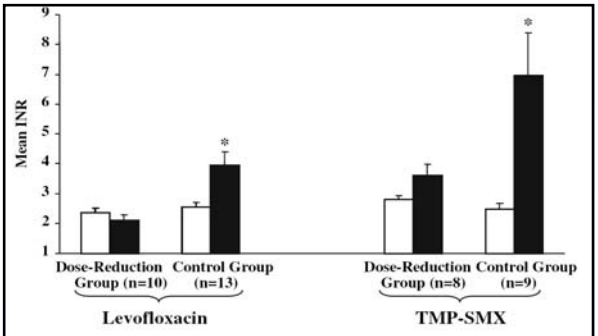

Fig. 1 Mean pre-antibiotic (empty bars) and post-antibiotic (black bars) INR values for the warfarin DR and control groups, for TMP-SMX- and levofloxacin-treated patients. *$P < 0.02$ vs. corresponding pre-antibiotic INR

Ahmed,et al

Clinical outcome	Dose reduction group ($n = 18$)	Control group ($n = 22$)	*P*-value
Interruption of warfarin dosing due to prolonged INR.	2 (11)	12 (55)	0.007
Administration of vitamin K	0 (0)	3 (14)	0.24
Administration of fresh frozen plasma	0 (0)	1 (5)	1.0

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

Ahmed , et al. J Thromb Thrombolysis 2008;26(1):44-8.

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?

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