New oral anticoagulant and antiplatelet drugs

Implications for the Gastroenterologist

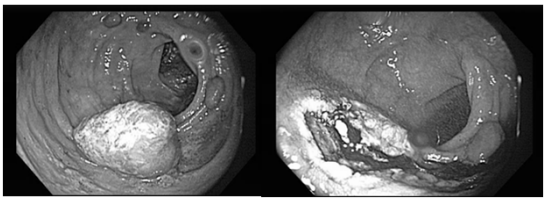
Dr. Daniel Sadowski
Royal Alexandra Hospital
Edmonton, Ab.

Disclosures

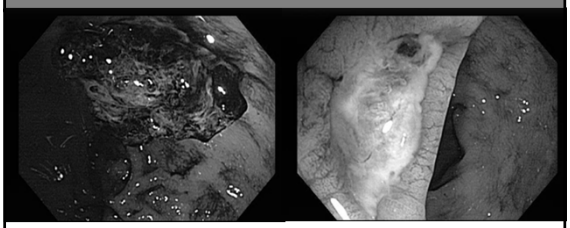
- No financial interests
- I am not a hematologist

Case

- 65 y.o. male referred for iron deficiency anemia (FIT positive)



Case: 6 days post-polypectomy



- When to restart dabigatran?
- Should I have held his ASA?
- Should I have used a different endoscopic technique?

Learning objectives

- Management of NOACS, platelet inhibitors in the setting of elective endoscopy
  - When to stop?
  - When to restart?
- Management of GI bleeding in the setting of NOAC and platelet inhibitor use

VIT K antagonists (coumadin/warfarin)

- Advantages:
  - Wide range of approved indications: DVT/PE, AF, mechanical heart valves, AMI
  - Reversible with Vit K and plasma, PCC's
- Disadvantages:
  - Monitoring required
  - Levels affected by dietary factors and other drugs
  - Narrow therapeutic window
  - Slow onset and offset

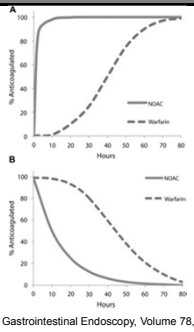
New Oral Anticoagulants

- Monitoring not required
- Stable anticoagulation levels
- Reversal not uniformly possible
- Agents:
  - Dabigatran (Pradaxa)
  - Riveroxaban (Xaralto)
  - Apixaban (Eliquis)
  - Coming soon:
    - Edoxaban (Lixiana -Japan) , Savaysa -US/Europe)

NOACs: Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Thrombin	Fxa	Fxa	Fxa
Half-life (h)	12-17	9-13	9-14	9-11
Dosing	110 – 150 mg bid	10-30 mg od	2.5-5 mg bid	15-30 mg od
Peak plasma conc.	2-3 h	2-4 h	1-3 h	1-3 h
Plasma protein binding	34-35%	92-95%	87%	40-59%
Renal elimination	80%	66%	25%	35%

Onset-Offset of Coagulation Effect



Gastrointestinal Endoscopy, Volume 78, Issue 2, 2013, 227 - 239

Bleeding vs. Thrombosis

	Low Procedural Bleeding Risk	High Procedural Bleeding Risk
Low risk of Thrombosis or Embolism	May continue anti-thrombotic agents	Stop anti-thrombotic agents
High Risk of Thrombosis or Embolism	Continue anti-thrombotic agents	Stop anti-thrombotic agents (consider bridge therapy)

High-risk Procedures	Low Risk Procedures
Polypectomy	Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including biopsy
Biliary or pancreatic sphincterotomy	ERCP without sphincterotomy
Pneumatic or bougie dilation	EUS without FNA
PEG placement	Enteroscopy and diagnostic balloon-assisted enteroscopy
Therapeutic balloon-assisted enteroscopy	Capsule endoscopy
EUS with FNA	Enteral stent deployment (without dilation)
Endoscopic hemostasis	
Tumor ablation by any technique	
Cystogastrostomy	
Treatment of varices	

Management of antithrombotic agents for endoscopic procedures *GIE 2009*

Risks of Thromboembolism

- Low
  - AF with CHADS2 Score 0-1
  - Bioprosthetic valve or mechanical mitral valve
  - Previous DVT
- Intermediate
  - AF CHADS2 score 2-3
  - DVT/PE in last 3-6 months
- High –? Use bridging?
  - Recent CVA/TIA
  - AF with CHADS2 4-6
  - DVT/PE in last 3 months
  - Mechanical Mitral Valve
  - Severe/multiple thrombophillic abnormalities
  - Recent placement of coronary stent

Periendoscopic management of NOAC's

Drug	Half-Life*	When to Stop**	Resume after***
Dabigatran	14 hours	2-5 days***	Low risk - Immediately High risk – at least 48 hours ERCP+sphincterotomy – 72 hours
Riveroxiban	8-12 hours	1-2 days	
Apixaban	8-15 hours	1-2 days	

*With normal Creatinine clearance
**3-5 plasma half lives = minimum wait time prior to endoscopy
Baron recommends holding Dabigatrin 5 days (7 with renal disease)

Clinical Comments:
Patients often forget that they are on these drugs
You must know the Creatinine Clearance
You must know how the patient is taking the drug. **36 hours after last dose.**

Adapted from Baron et al.NEJM 2013

Practical considerations

- All NOAC's have a rapid onset of action: 1-3 hours
- Patients need to be informed about late (7-14 day) bleeding risk for colonic polypectomy
- For patients at high risk of delayed bleeding (e.g. removal of large sessile polyps requiring extensive electrocautery) – hold NOAC for 5-7 days

Practical considerations

- Consider biliary stent without sphincterotomy for patient on a NOAC who require urgent ERCP (e.g. biliary sepsis)
- Bridging:
  - No current clinical evidence
  - Scenarios:
    - Dabigatran requiring >5 days held pre-procedure
    - High risk for post-procedure bleeding
  - No uniform recommendation on drug dosing
    - When to start LMWH
    - What drug to use post-procedure (NOAC, LMWH)

Anti-platelet agents - periendoscopic management:

Agent (ADH Inhibitors)	Stop when?	Restart when?	Time to maximal platelet inhibition
Aspirin	Continue for all procedures	-	
Aspirin/dypyridamole (Aggrenox)	7-10 d *?start ASA?*	1 d	7 days
Clopidogrel (Plavix)	5 d	1 d	3-5 days (consider loading dose 600 mg)
Prasugrel (Effient)	7 d	1-2 d	4 hours
Ticagrelor (Brilinta)	5 d	1-2 d	4 hours

Adapted from Baron T, NEJM 2013

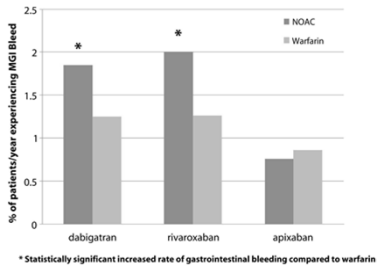
Glycoprotein IIb/IIIa inhibitors

- Used in acute coronary syndromes
- IV only
- Reversible platelet inhibition
- Very short anticoagulation effect
- Agents:
  - Abciximab (Reopro)
  - Eptifibatide (Integrilin)
  - Tirofiban (Aggrastat)

Anti Platelet agents: Clinical Caveats

- Continue ASA even in high risk procedures
- Most patients are on dual antiplatelet therapy for a drug eluting stents
- Exercise caution in discontinuing therapy:
  - Within 6 weeks of bare metal stent insertion
  - Within 3-6 months of drug eluting stent insertion
  - Consider delay of procedure?
- Platelet transfusions:
  - Could provoke stent thrombosis when used in bleeding after GP IIIa drug

NOACs and GI Bleeding



The rate of major GI bleeding in the 3 pivotal novel oral anticoagulant trials

Gastrointestinal Endoscopy 2013;78:p227 - 239

NOAC's in Acute GI bleeding

Drug	PTT	TT	Consider	With uncontrolled bleeding*
Dabigatrin	⇧	⇧	Hemodialysis, charcoal HP, activated charcoal	aPCC (FEIBA) – 50-100 U/kg
Riveroxiban	⇧	⇧	Charcoal HP, activated charcoal, rapid gut lavage	PCC (Octaplex, Beriplex) 50 U/kg or FEIBA or rFV11A
Apixaban	±	±	Hemodialysis ineffective	?unknown? Same as for Riveroxiban?

*PCCS, FEIBA, rFVIIa – have only been studied in healthy non-bleeding volunteers

GI Bleeding: practical considerations

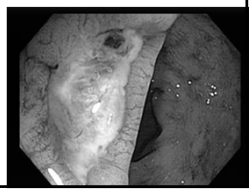
- Most important info:
  - When was the last dose? What is the PTT?
- Time is your friend (resuscitation will enhance renal drug excretion)
- The hematologist on call is also your friend
- BUT: urgent endoscopy and endoscopic therapy should be performed in the unstable bleeding patient even if patient is fully anti-coagulated.

GI Bleeding: practical considerations

- Reversal agents (PCC's, FEIBA, rFVIIa) increase thrombotic risk
- Consider platelet transfusion
- Coming soon - humanized dabigatran-specific (Fab) antibody antidote

Case

- ASA – continue
- Dabigatran – hold for longer than 3-4 days?
- Bridge post-procedure with LMW heparin?
- Cold snare polypectomy for smaller polyps?
- Mucosal closure?



For further reading:

- Parth J. Parekh et al New Anticoagulants and Antiplatelet Agents : A Primer for the Clinical Gastroenterologist. *Am J Gastroenterology 2014; 109:9 – 19*
- Abraham NS. Novel Anticoagulants: bleeding risk and management strategies. *Current Opinion in Gastroenterology 2013;29:6*
- Baron TH. New Anticoagulant and Antiplatelet agents. *CGH 2014;12:187-195*

- Discussion and Questions