Anticoagulation: What keeps the GI team busy!

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EDUCATIONAL AIMS: ANTICOAGULATION

1. The old and the new
2. Elective patient peri-procedural management
3. The acute bleed

BACKGROUND

- Anticoagulants and antplatelet agents: some of the commonest causes of death and morbidity need to be prescription drugs.
- Used appropriately: some of the most beneficial pharmacological agents we have.
- Aging population and increasing trial data showing benefit: increasing numbers of older patients will be on blood thinners.
- This intersects with our lives in GI as increasing numbers of older patients undergo endoscopic procedures.
- Pharmacology is complicated and many factors need to be considered in the optimal management of each patient.

IT IS NOT SO SIMPLE ANYMORE: ONE SIZE DOES NOT FIT ALL.
ANTITHROMBOTICS

- Anti-platelet agents
- Anti-coagulants

Why are patients on anti-thrombotic agents?
- Peripheral vascular disease
- Atrial Fibrillation and cardiomyopathy
- Mechanical heart valves (Aortic and mitral)
- Thromboembolic disease: DVT, PE, orthopedic joint replacement prophylaxis, other.
- Vascular stents: coronary, peripheral, aortic

IT USED TO BE SO EASY

- Aspirin (+/- Asasantin: Aspirin + Dipyridamole)
- Warfarin
- Heparin including the more recent weight based low molecular weight heparins (LMWH)
Now what a mess!

- Antiplatelet agents:
  - Clopidogrel (Plavix)
  - Effient
  - Brilinta

- Anticoagulants: NOACS
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)

INTRODUCTORY CASES: CASE 1

78 year old male presents with melena and pre-syncope.

Background: hypertension & coronary stenting: drug-eluting stents x3 placed 12 months ago (Prior acute MI – no angina).

- On Aspirin and Effient (Prasugrel).
- BP 90, HR 80 (remember β-blockers may mask the tachycardia response).
- Upper endoscopy + colonoscopy ~12 months ago: reflux and diverticulosis.
- HB 70, Urea 16.

Transfused 7U of packed cells: remains unstable.

What is the next step?

- CT bleeding study
- Angiogram + embolization
ISSUES RAISED CASE 1
- Can we cease the Aspirin and Effient?
- If so which one and for how long?
- When do we restart?

INTRODUCTORY CASES: CASE 2
- 70 year male for colonic polyp surveillance.
- On Aspirin for stable ischemic heart disease.
- Also on Imuran: autoimmune disease.
- Colonoscopy: large hepatic flexure adenoma removed with hot snare following fluid Ad lift.
- Post-EMR clip prophylaxis: Instinct (Cook) x7
ISSUES RAISED CASE 2

- Should we cease Aspirin pre-elective procedures?
- Should we cease the Aspirin once he bled?
- Prophylactic clipping / mechanical intervention.
- Management of bleeding complications

INTRODUCTORY CASES: CASE 3

56 year old patient with mechanical AVR.
- Presented for ERCP and CBD stone.
- Warfarin ceased pre-procedure and changed to Clexane 80mg BD (LMWH); weight based dosing 80kg (1mg/kg BD or 1.5mg/kg OD).
- Successful ERCP and duct clearance.
- Re-anti-coagulated after 24hrs. Therapeutic Clexane.

- Day 3 melena, Hb drop to 110 and urea bump
- Repeat endoscopy with side viewer:
ISSUES RAISED CASE 3

- Peri-procedural anticoagulation with prosthetic heart valves.
- When do we restart therapeutic anticoagulation?
- Hemostasis management?

RESTRICTIVE TRANSFUSION

RISK - BENEFIT EQUATION
CHADS SCORE: STROKE RISK IN AF

WHAT ARE THE BLEEDING RISKS?

DIAGNOSTIC ENDOSCOPY

- No clinical trials demonstrate increased incidence of bleeding in patients undergoing upper or lower endoscopy or biopsy while taking Aspirin or Clopidogrel.
- Continuing therapeutic anticoagulation (warfarin) during peri-procedural period: low risk of bleeding in low-risk procedures.
- Retrospective endoscopic study (Gerson et al): 28/104 patients (171 procedures) maintained therapeutic warfarin dosing. In low-risk upper endoscopy / colonoscopy including biopsy, no clinically evident bleeding occurred.

POLYPECTOMY

- Several studies of antithrombotic therapy in post-polypectomy bleeding.
- Prospective studies of low risk patients: increased risk of post-polypectomy bleeding if taking aspirin or NSAIDs. Of larger retrospective studies:
  - Very large studies would be required.
  - Continuing therapy is safe (but not without risk).
  - Post-polypectomy bleed risk increased if taking warfarin, resuming warfarin / heparin within 1 week.
- Case series of prophylactic clip application after polypectomy of polyps <1 cm in patients taking antithrombotic agents: low rates of bleeding (0% - 3.3%).
- No randomized controlled trials. Cost-benefit analysis.
- Routine prophylactic application of clips: detachable snares not recommended at this time. “Feeling in my waters.”
SPHINCTEROTOMY AND PEG

- Risk of post-sphincterotomy bleeding is 0.3% to 2.0%.
  - Withholding aspirin or NSAIDs up to 7 days before sphincterotomy: does not reduce bleeding risk.
  - Oral warfarin / intravenous heparin within 3 days increases risk of post-sphincterotomy bleeding.
- PEG placement: bleeding complication rate of ~ 2.5%.
  - The risk of bleeding for PEG placement in the patient receiving antithrombotic therapy is unknown.

REVERSAL OF WARFARIN

- Avoid Vitamin K to reverse anticoagulation prior to elective procedures.
  - Delays therapeutic anticoagulation.
- The 2006 American College of Cardiology (ACC) guidelines:
  - Low risk thrombosis: withhold pre-procedure (3-5 days). Heparin antithrombotic therapy usually unnecessary.
  - Risk of embolism event and patients in whom anticoagulation is delayed: 4-7 days ~ 1%.
  - Large prospective trial of anticoagulation: ~58% cases of warfarin interruption.
  - Atrial fibrillation (43%), venous thrombosis (11%), and mechanical heart valves (10%).
  - 10 patients had risk of thrombosis with 80% of the patients 1-2% risk.
  - 6.6% of the total study population had anticoagulation for less than 3 days.
  - 7.6% patients had a post-procedure thromboembolic event within 30 days.
  - Those receiving bridging therapy: 3 patients were high risk, active malignancy, recent DVT.
- 4% of the 23 patients with peri-procedural bleeding event on bridging therapy with heparin.

BRIDGING HEPARIN THERAPY

- AIM: reduce the risk of thromboembolic events in patients on warfarin.
  - Switch to a shorter-acting heparin-based therapy in the peri-procedural period.
- Evidence limited on unfractionated heparin (UFH) and low molecular weight heparin (LMWH) as bridging therapy for endoscopic procedures.
  - One study: 38 patients undergoing antiplatelet therapy with bridging therapy with LMWH in the peri-procedural period.
  - 2/38 patients had minor procedure bleeding, none had major procedure bleeding.
  - 2/38 patients had major procedure bleeding without bridging therapy with UFH.
RESTARTING

Optimal timing for resumption of antithrombotic therapy after endoscopic intervention.

- Benefit of immediate re-initiation to prevent thromboembolic events vs. bleed risk.
- Procedure-specific circumstances (sphincterotomy, polypectomy, or endoscopic mucosal resection).

1 study: 84 patients in 109 colonoscopies (47% hot biopsy or snare polypectomy), patients were instructed to restart warfarin therapy immediately after the examination.

- 10.64% rate of procedure-related bleeding 7 days into warfarin therapy: hospitalization and transfusion.
- None of the patients undergoing diagnostic colonoscopy experienced bleeding.

Second study involving 173 patients found that resuming warfarin or heparin within 1 week after polypectomy was associated with increased risk of bleeding (odds ratio 5.2; 95% CI, 2.2-12.5).

THE NEW DRUGS

- Warfarin has been the mainstay of anticoagulation for 50 years.
- Why are there these new agents: WARFARIN not perfect.
  - Narrow therapeutic window (INR: 2-3.5)
  - Monitoring with secondary cost
  - Narrow safety margin for complication
  - Slow onset-offset
  - Interactions: dietary and medications
WARFARIN: ADVANTAGES

- Well established – everyone is aware.
- Easily reversed:
  - Vitamin K
  - Fresh frozen plasma (FFP)
  - Prothrombin complex concentrates
- Bridging therapy with heparin well established

Risk Factors for Major Bleeding On Warfarin

- Age >70 years old
- Bleeding disorder
- Gastrointestinal hemorrhage last 18 months
- Previous stroke
- Liver disease
- History of falls

Marked increase in risk
- Age >70 years old
- Bleeding disorder
- Gastrointestinal hemorrhage last 18 months
- Previous stroke
- Liver disease
- History of falls

Moderate increase in risk
- Age 60-70 years old
- Chronic renal failure
- Change in interacting medications
- Change in, or poor, nutrition
- First three months of warfarin therapy
- Large fluctuations in INR

THE NEW ANTICOAGULANTS: NOACs

- Pradaxa: Dabigatran
- Xarelto: Rivaroxaban
- Eliquis: Apixaban

At least as effective as Warfarin
Indicated: thromboembolic disease, stroke prophylaxis in atrial fibrillation
No need for monitoring
### SUMMARY TABLE

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<th>Target Protein</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tr>
<td>Pro-Drug</td>
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<td>Factor Xa</td>
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<td>aPTT, Anti-factor Xa</td>
</tr>
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</table>

#### REVERSAL: NEW ANTICOAGULANTS

- Universal Xa antidote (PRT4445) in Phase 2 trials
- FFP: No data, unclear/unknown benefit
- 3 factor Prothrombin Complex Concentrates (PCC): Unknown
- 4 factor PCC: Reverse Rivaroxaban but not Dabigatran
- Recombinant Factor VIII: Case reports only – EXPENSIVE ($10 000/patient)

- Risk of arterial thrombosis
  - PCC's and RVIIa increase risk of arterial thrombotic events in non-hemophilic patients
  - Must weigh potential risks with potential benefits

- Standard tests are often abnormal – useful for determining absence of residual drug when normal.
- Abnormal clotting tests do not reflect degree of anticoagulation. INR is of no value for monitoring therapy.
DABIGATRAN: Pradaxa

- D/I: Renal excretion
- NOT REVERSIBLE: FFP and PCC’s have no role
- Cease 2 days prior to high bleeding risk procedure: normal renal function
- Some institutions: more conservative: Mayo Clinic
  - Cease 5 days prior CrCl/30-50ml/min; 7 days prior CrCl <30ml/min
  - Emergency ERCP: allow no cut
  - Active GI bleeding: withhold and support.
  - Pack cell, endoscopic hemostasis +/- embolization; ICU support - hemodialysis, charcoal hemoperfusion
  - rFVIIa, FEIBA for ongoing severe bleeding; last resort and caution

RIVAROXABAN: Xarelto

- D/I: Renal excretion: Do not use in Childs B/C cirrhotic or severe renal impairment
- NOT REVERSIBLE: FFP has no role
- Cease 8 days prior to high bleeding risk procedure: normal renal function
- Some institutions: more conservative: Mayo Clinic
  - Cease 3 days prior CrCl/30-50ml/min; 5 days prior CrCl <30ml/min; allow for 7 days
  - Emergency ERCP: allow no cut
  - Active GI bleeding: withhold and support.
  - Pack cell, endoscopic hemostasis or embolization; ICU support - hemodialysis, charcoal hemoperfusion
  - 4 Factor PCC, FEIBA for ongoing severe bleeding: last resort and caution

APIXABAN: Eliquis

- D/I: less dependent on renal excretion: otherwise advice as per Rivaroxaban
- In Australia shift to Apixaban from Dabigatan – recent meta-analysis 2012: lower rate of major and GI bleeding
- NOT REVERSIBLE: FFP has no role.
- Cease 2 days prior to high bleeding risk procedure
WHEN TO RESTART ANTICOAGULANTS

The balance of risk.

- Low risk: 24 hours
- High risk: 48 hours
- Highest risk:
  - Sphincterotomy: 72 hours
  - Large polypectomy (EMR / ESD): 7 days
- Remember we can always bridge with heparin.

REMEMBER: RISKS OF NEW DRUGS

- Pradaxa may cause serious internal bleeding and heart attacks.
- Call 1-800-BAD-DUG.
ANTIPLATELET THERAPY:
BACKGROUND

- Coronary stents: Bare metal and Drug Eluting
  - Single agent Vs Dual AP Therapy
  - If therapy ceased inappropriately: stent thrombosis with high mortality risk:
    - Bare metal: within first 6 weeks
    - Drug eluting: 3-6 months after placement
    - Liaison with cardiologist essential

ASPIRIN

THE NEW KIDS ON THE BLOCK

- Clopidogrel (Plavix)
- Prasugrel (Effient)
- Ticagrelor (Brilinta)
  - Oral agents
  - Adenosine diphosphate receptor-P2Y12 inhibitors
  - ADP-P2Y12 Receptor Antagonists
**PLAVIX**
- Hepatic metabolism: drug interaction with proton pump inhibitors.
- 1/3 of platelets are out of action within 48hrs
- 60% by 1 week
- Increases risk of post-procedural bleeding particularly with dual therapy with aspirin.

**EFFIENT**
- Hepatic metabolism – no risk of drug interaction with proton pump inhibitors.
- 10-100x more potent platelet aggregate inhibitor than Plavix
- Rapid on set of action
- Non-reversible: lifespan of platelets is 10-11 days.
- Once stopped 10% of platelets are regenerated / day

**BRILINTA**
- Rapid onset and offset of platelet inhibition
- Once ceased antplatelet inhibition rapidly declines over 72 hr: near normal at 5 days.
OVERVIEW ORAL ANTIPLATELETS

New anticoagulant and antiplatelet agents: a primer for the gastroenterologist.

ACUTE BLEEDING AND RESUMPTION

- With all three acute bleeding requires supportive care as effects wear off: platelet transfusion is not completely effective
- Not one size fits: influenced by the procedure performed, concurrent Aspirin, cardiac nuances.
- Discuss with cardiologist appropriate.

CONCLUSION

- Knowledge of these old and new drugs is essential.
  - Procedural bleeding risk minimization.
  - Acute GI bleed management.