ANTICOAGULANTS: THE QUICK GUIDE TO USE AND REVERSAL

Thomas G. DeLoughery, MD MACP FAWM
delought@ohsu.edu

ANTIPLATELET AGENTS

Aspirin
Use: primary (only very high risk patients) and secondary prevention of myocardial infarction, secondary prevention of stroke, therapy of peripheral vascular disease
Dose: 81mg chronic, ≥160mg acute therapy loading dose
Pediatric: 6-20mg/kg/day
Reversal: desmopressin, platelet transfusion - one pheresis unit (may worsen outcomes in ICH)

Clopidogrel:
Use: along with aspirin: prevention of MI, acute coronary syndromes, and with coronary stents
Dose: 75 mg per day (bolus 3-600 mg)
Pediatric:???
Reversal: Desmopressin (?), platelet transfusions - two pheresis units

Prasugrel:
Use: along with aspirin: acute coronary syndromes with interventions
Dose 60 mg loading, 10mg daily (consider 5mg in patients < 60 kg or over age 75)
Pediatrics: ??
Reversal: Desmopressin (?), platelet transfusions - - two pheresis units

Ticagrelor:
Use: along with aspirin: acute coronary syndromes
Dose: 180mg load the 90mg bid
Reversal: Desmopressin (?), platelet transfusions - - two pheresis units(??may be ineffective)

Sustained Release Aspirin/Dipyridamole
Use: secondary prevention of stroke
Dose: 1 bid
Reversal: desmopressin, platelet transfusions

Vorapaxar (thrombin receptor inhibitor)
Dose 2.5 mg bid
Indication: recent myocardial infarction
Reversal:?

GPIIB/IIIA INHIBITORS

Odd side effect: thrombocytopenia in 1% and severe in 0.5% - can occur with in 2 hour of dose. Responds to platelet transfusion.

Abciximab
Use: Adjunct to percutaneous coronary interventions
Dose: 0.25Mg/kg plus 0.125 Ug/kg/min (maximum 10 ug/min) for twelve hours after PCTA
Heparin: 70 units/kg (maximum 7000 units) bolus with additional bolus to achieve an ACT of 200 seconds.
Reversal: platelet transfusions

Eptifibatide
Use: adjunct to percutaneous coronary interventions and unstable angina
Acute coronary syndromes: bolus 180 ug/kg followed by a continuous infusion of 2ug/kg/min until resolution of patient, procedure or 72 hours. For percutaneous coronary intervention during acute syndrome decrease infusion to 0.5Ug/kg/min and continue for 24 hours after procedure.
Percutaneous coronary intervention (non-acute): bolus with 135 ug/kg follow by a continuous infuses for 20-24 hours.
ESPRIT PCI dosing:180 ug/kg bolus then 2ug/kg/min for 18-24 hours. Second 180 ug/kg bolus ten minutes after the first.
Reversal: platelet transfusions plus infusion of cryoprecipitate

Tirofiban
Dose: 0.4Ug/kg/min for 30 minutes then an infusion of 0.1Ug/kg/min until resolution of the pain syndrome or for 12-24 hours after angiography. Patients with creatinine clearance under 30 ml/min should receive one-half dose
Give with aspirin and heparin
Reversal: platelet transfusions plus infusion of cryoprecipitate

HEPARIN AND HEPARIN LIKE AGENTS
Background: Acute therapy and prevention of venous and some arterial thrombotic disease. All work via antithrombin.

Heparin
Background: slowly being replaced by more specific agents.
Route of administration: Subcutaneous or intravenous
Prophylactic: 5,000 units bid or tid
Therapeutic: Bolus 5-10,000 units followed by 1-2,000 units/hour to achieve heparin levels of 0.35-0.7 anti-Xa units
Pediatric: Bolus 75 units/kg then < 1 year: 28 units/kg/hr, > 1 year : 20 units/kg/hr

Reversal: Protamine:

Time since last heparin dose	**Dose of Protamine**
< 30 minutes	1 unit/100 units of heparin
30-60 minutes	0.5 - 0.75 units/100 units of heparin
60-120 minutes	0.375 - 0.5 units/100 units of heparin
> 120 minutes	0.25 - 0.375 units/100 units of heparin
Infusion	Add units of heparin infused during last hour - then 1 unit protamine/100 units of heparin

Infusion rate should not exceed 5 mg/min. Maximum dose is 50 mg

Odd side effect: Heparin induced thrombocytopenia in 1-5% of patients.

Low Molecular Weight Heparin
Background: Shown to be safer and more effective than standard heparin for acute therapy for deep venous thrombosis and is safe and effective for therapy of pulmonary embolism.

Reversal of Bleeding: Protamine (works just as well with LMWH as heparin) - if with-in 4 hours of dose 1mg of protamine for each 1mg of enoxaparin or 100 units of daltaparin and tinzaparin. Should repeat one-half dose in 4 hours. If 4-8 hours after dose give 0.5 mg for each 1 mg of enoxaparin or 100 units of daltaparin and tinzaparin.
Odd side effect: Heparin induced thrombocytopenia in <1% of patients.

Specific LMWHs

Daltaparin
Prophylactic: 2500 units qday (low risk); 5000 units q day (high-risk abdominal surgery)
Therapy: 100 units/kg every 12 hours or 200 units/kg daily

Enoxaparin
Prophylactic: 40 mg/day or 30 mg every 12 hours (orthopedic or trauma indications)
Therapy: 1mg/kg every 12 hours or 1.5 mg/kg in low risk patients
Pediatrics: < 5 kg: 1.5 mg/kg q12 hours, > 5 kg: 1mg/kg q 12 hours

Tinzaparin
Prophylactic: 3500 units every 24 hours (4500 units in high risk patients)
Therapy: 175 units every 24 hours

Specific Pentasaccharide
Fondaparinux
Prophylaxis: 2.5 mg every 24 hours
Therapy: 7.5 mg every 24 hours (consider 5.0 mg in patients under 50kg and 10 mg in patients over 100 kg)
Reversal: Protamine ineffective - 4 factor PCC 50 units/kg

DIRECT ORAL ANTICOAGULANTS

Direct thrombin inhibitor

Dabigatran
Pharmacology
Time to maximum concentration: 1-2 hours
Half-life: 12-17 hours
Renal elimination: 80%
Dosing:
Prophylaxis 220mg or 110mg dDay
Venous thrombosis treatment: 150 mg BID (acute thrombosis after 5 days parenteral heparin)
Stroke prevention atrial fibrillation: 150 mg BID
Renal clearance: dose reduce to 75mg bid if CrCl < 30 and contraindicated CrCl < 15
Affects aPTT - can use to see if patient still has drug effect – 1.5 -2x 0.5-2 hours after dose
Drug-drug interaction – P-gp inhibitors: Dronedarone, ketoconazole - dose reduced to 75mg bid or contraindicated if renal impairment. P-gp inducers: Rifampin, St John's wort - contraindicated.
Reversal agent: Idarucizumab 5 grams IV

Factor Xa Inhibitors

Apixaban
Pharmacology
Time to maximum concentration: 3-4 hours
Half-life: 12 hours
Renal elimination: 25%
Dosing
Prophylaxis 2.5mg BID
Venous thrombosis treatment: Initial treatment for acute thrombosis of 10mg bid x 7 days then 5mg bid, contraindicated it CrCl < 25.
Stroke prevention atrial fibrillation: 5mg BID

2.5 BID if 2 out of the three: age over 80, creatine > 1.5, weight less than 60kg -contraindicated with CrCl < 15

Drug-drug interaction: CYP 3A4 agents (azole antifungals (except fluconazole) or HIV-protease inhibitors) - reduced dose to 2.5mg BID

Does not affect INR - use anti-Xa or specific levels to monitor

Reversal agent: PCC 50 units/kg or Andexanet 400mg IV bolus then 4mg/min for 120 minutes (if 10mg apixaban dose within 8 hours then 800mg IV bolus followed by 8 mg/min for 120 minutes)

Betrixaban

Pharmacology

Time to maximum concentration: 3-4 hours

Half-life: 19-27 hours

Renal elimination: 20%

Dosing

Prophylaxis: First day 180mg then 80mg daily for 35-42 days

Drug-drug interaction: P-gp inhibitors - cut dose by 50%

Does not affect INR/aPTT - use anti-Xa or specific levels to monitor

Reversal: PCC 50 units/kg

Edoxaban

Dosing

Prevention: 15 mg/day

Thrombosis therapy: 60mg/day or 30mg/day if weight < 60kg, CrCl 30-60, or on strong P-gp inhibitors.

Stroke Prevention in Atrial Fibrillation: 60mg/day or 30mg/day if weight < 60kg, CrCl 30-60, or on strong P-gp inhibitors.

Drug-Drug interactions: dose reduced 50% -verapamil, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole. Contraindicated - protease inhibitors and cyclosporine

Affects INR - use anti-Xa or specific levels to monitor

No specific antidote: PCC 50 units/kg

Rivaroxaban

Pharmacology

Time to maximum concentration: 2-4 hours

Half-life: 5-9 hours

Renal elimination: 66%

Dosing

Prophylaxis 10mg qD

Therapy venous thrombosis: DVT 15mg BID x 3 wks then 20mg/day, contraindicated CrCl < 30

Stoke prevention in atrial fibrillation 20 mg/day - dose reduce to 15mg/day CrCl 50-15

Drug-drug interaction: CYP 3A4 agents (azole antifungals (except fluconazole) or HIV-protease inhibitors)

Affects INR - use anti-Xa or specific levels to monitor

No specific antidote –PCC 50 units/kg or Andexanet 800mg IV bolus then 8mg/min for 120 minutes (if > 8 hours since dose then 400mg IV bolus followed by 4 mg/min for 120 minutes)

THROMBOLYTIC THERAPY

Reversal: Immediate infusions of equivalent of 6-8 units of platelets (or one platelet pheresis product), 2 units of plasma, and 10 units of cryoprecipitate. No value in infusing anti-fibrinolytic agents

Anistreplase

Myocardial infarction-30 units iv over 5 minutes.

Reteplase
Myocardial infarction -two 10 units bolus separated by 30 minutes.

Streptokinase
Myocardial infarction-intravenous: 1.5 Million units over one hour. Intracoronary infusion: 20,000 unit bolus followed by 2,000 units/minute for one hour.
Pulmonary embolism: 250,000 unit load over 30 minutes then 100,000 units/hour for 24 hours.
Deep venous or arterial thrombosis: 250,000 unit load over 30 minutes then 100,000 units/hour for 24-72 hours.
Odd side effect: hypotension, allergic reactions

Tissue plasminogen activator (alteplase)
Myocardial infarction- 15 mg/kg bolus, 0.75Mg/kg over 30 minutes (not to exceed 50mg), then 0.5 Mg/kg (not to exceed 35 mg) over next hour. Total dose should not exceed 100 mg.
Stroke- 0.9Mg/kg (maximum 90 mg) over one hour with ten percent of the dose given in one minute.
Pulmonary embolism - 100 mg given over 2 hours

Reteplase
Myocardial infarction: two 10 unit boluses separated by 30 minutes.

Tenecteplase
Myocardial infarction: weight-based bolus over 5 seconds.
<60 kg = 30mg
60-69 kg = 35mg
70-79 kg = 40mg
80-89 kg = 45mg
>90 kg = 50mg

Urokinase
Pulmonary embolism - 4400 units/kg over one minute load then 4400/kg/hour for 12 hours.
Arterial thrombosis - 4000 units/minute for four hours then 2000 units/minute for up to 44 hours

WARFARIN
Uses: Standard therapy for chronic therapy of DVT/PE and prevention of embolism in patients with atrial fibrillation or mechanical heart valves
Dose: varies greatly dependent on age, other med, genetics – see nomograms
Loading Dose:
10 mg: age < 60 and albumin > 3.5
5 mg: Age 60-70
2.5 mg: age > 70
Reversal: see below
Odd side effect: warfarin skin necrosis - seen in patients with **acute** thrombosis started on warfarin with no heparin coverage. Results in necrosis of large areas of the skin.
Genetics: no benefit yet of using genotypes to dose warfarin

Therapy of the Bleeding Patient on Warfarin
Key point about vitamin K
● sub-Q erratic and should **NOT** be used
●PO effective in most patients
●IV should be given slowly (over one hour)
● A little goes a long way - the RDA is 80 ug/day

Not Bleeding: Goal is INR in 2-3 range

INR	Action
3-3.45	Hold dose until INR decreased
4.5-10	1.25 mg Vitamin K PO
> 10	2.5 -5 mg Vitamin K PO

Should see INR back in therapeutic range in 24-48 hours

Bleeding: Goal is INR under 2

INR	Action
2-4.5	2.5 mg Vitamin K ± FFP (15ml/kg)
4.5-10	5 mg Vitamin K ± FFP (15ml/kg)
>10	5-10 mg Vitamin K ±FFP (15ml/kg)

Consider Intravenous route for Vitamin K if faster effect desired

Use Prothrombin Complex Concentrates for life-threatening bleeding such as intracranial hemorrhage - dosing:
If INR 2-4: 25 units/kg (not to exceed 2500 units)
If INR 4-6: 35 units/kg (not to exceed 3500 units)
if INR > 6: 50 units/kg (not to exceed 5000 units)