

Basic principles and monitoring of new anticoagulants and anticoagulant reversal

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New Anticoagulants

Therapeutic manipulation of the hemostatic system

- Anticoagulants – thrombin/fibrin generation
- Fibrinolytic agents – clot lysis
- Anti-platelet agents – prevention of arterial thrombosis

Anticoagulants

- Treat and prevent venous thrombosis
- Prevent intracardiac clot formation in patients with structural/functional heart problems eg atrial fibrillation, prosthetic heart valves
- Auxiliary agent in short term prevention of myocardial infarction

Therapeutic manipulation of the hemostatic system

Anti-coagulants

- Warfarin
- Heparin
- Low molecular weight heparin
- Heparin pentasaccharide
- Lepirudin
- Danaparoid

Limitations of current anticoagulants

- Warfarin
 - narrow therapeutic window,
 - Slow onset/offset
 - drug interactions,
 - INR monitoring, unpredictable dosing
 - bleeding,
 - initial prothrombotic effect
- Heparin
 - Unpredictable, HITTS
- LMWH
 - bd or daily injections,
 - small potential for HITTS
 - Residual VTE rate in prophylaxis

Ideal properties of new anticoagulants

- Orally active
- Predictable dosing
- Low bleeding rate
- Easily reversible (or short action)
- No side effects
- No interactions with other drugs

**New anticoagulants likely to be in
routine use soon**

Indirect Factor Xa inhibitors

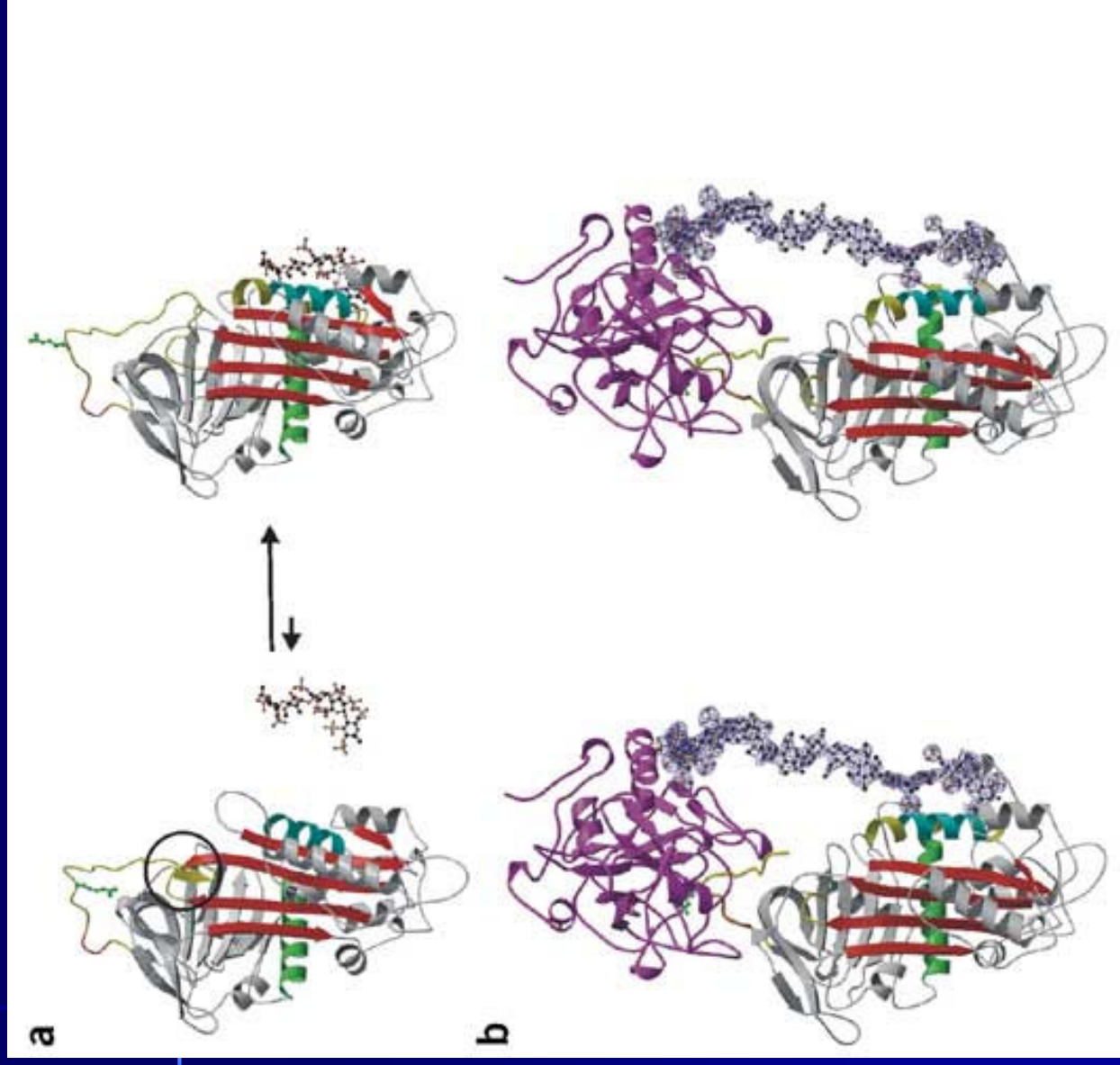
Direct Xa inhibitors

Direct thrombin inhibitors

Indirect Factor Xa inhibitors

- Heparin pentasaccharide
 - fondaparinux
- Long acting pentasaccharide
 - Idraparinux
- Biotinylated long acting pentasaccharide
 - Biotinylated idraparinux

Antithrombin activation by heparin



Heparin pentasaccharide

Long chain heparin

Heparin pentasaccharide fondaparinux

- DVT/PE treatment – equivalent to enoxaparin/warfarin
- VTE prevention – orthopedic surgery, superior to enoxaparin

Long acting pentasaccharide idraparin

- Hypermethylated derivative of fondaparinux
- High affinity for antithrombin
- Terminal half life of 200 hr

Long acting pentasaccharide idraparinux

- Van Gogh studies for DVT and PE compared to enoxaparin/warfarin
- DVT – equivalent recurrence and bleeding at 6 mth
- PE – excess death and symptomatic PE recurrence (all in first 2 weeks)
- Amadeus study AF (idraparinux vs warfarin)
 - study terminated, excess bleeding in idraparinux arm

Biotinylated idraparinux

- Biotinylated idraparinux - identical PK/PD to idraparinux
- Anticoagulant activity of biotinylated idraparinux completely reversed by IV avidin

Biotinylated idraparinux

- Equinox study – comparison of idraparinux with biotinylated idraparinux in DVT
- Cassiopea study – comparison of biotinylated idraparinux with enoxaparin warfarin after an initial open label 5-10 days enoxaparin

Direct Factor Xa inhibitors

Rivaroxaban, apixaban

- Small molecules which bind with high affinity to Factor Xa active site
- High oral bioavailability, not prodrugs
- Half life 8-10 hr
- Apparent wide therapeutic window

Direct Factor Xa inhibitors

- Currently in phase III studies in DVT prevention (orthopedic) and DVT treatment show flat dose response
- Also in clinical studies for AF and acute coronary syndromes

Direct thrombin inhibitors

- Hirudin and analogues known to be effective anticoagulants
- Expensive
- Short half life
- Renal excretion

Direct thrombin inhibitors – small molecule

- Ximelagatran - prodrug metabolised to melagatran
- Completed phase III studies in VTE prevention and treatment and AF
- Efficacy as good as or better than standard of care

Direct thrombin inhibitors – small molecule

- Abnormal LFT
- Transaminases >3x ULN 7.9%
- Bilirubin >2x ULN 0.5%
- Small number of liver failure/death
- Development terminated

Direct thrombin inhibitors – small molecule

- Dabigatran etexilate
- Orally active thrombin inhibitor
- Minimal potential for drug interactions
- ALT > 3x ULN 1.5% in early studies
- Currently in Phase III prevention and treatment trials

New anticoagulants

- All new anticoagulants in development are dosed independent of body weight with no monitoring required

Novel agents

- Beta-D-xyloside – odiparcil
- Dose dependent induction of production of endogenous glycosaminoglycans with dermatan sulphate-like activity
- Activates heparin cofactor II
- Produces thrombin inhibitor effect
- No change in INR/APTT
- Currently in Phase II trial in total knee replacement

Conclusions

- Multiple new agents with potential for improved convenience and effectiveness
- Likely to be relatively expensive
- Awaiting results of Phase III studies for registration

Anticoagulant reversal

Anticoagulant reversal

- In practice this refers to warfarin reversal
- Reversal of LMWH rarely required
- Reversal of heparin usually applies to cardio-pulmonary bypass

Situations where warfarin reversal may be required

Elevated INR without bleeding

Therapeutic or elevated INR with bleeding

Peri-operative management of warfarin anticoagulation

Risk of bleeding

Close relationship with INR
Increases noticeably once INR exceeds 4,
and rises sharply with values greater
than 5

THE INR

- Bleeding risk has a close relationship with

INR

- Bleeding risk increases exponentially from INR 5 to 9

INR \geq 6 should be monitored closely

Limitations of INR as indicator of bleeding risk

- 50% of bleeding episodes still occur with INR < 4

INR IS A GUIDE OF BLEEDING RISK BUT NOT AN ABSOLUTE INDICATOR