I. Direct Oral Anticoagulants (DOACs):
Introduction

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Oral Anticoagulation - Purpose

Oral anticoagulation indications:
Patient has thrombosis (clot) - treatment
Patient at risk for thrombosis – prophylaxis

Most common oral anticoagulant: Warfarin – a vitamin K antagonist
Coumadin®/Jantoven® are brand names for warfarin
Reduces the amount of functional vitamin K dependent factors
Factors II, VII, IX, X, Protein C and Protein S
Full anticoagulant effect takes days
Episodic monitoring required
Dietary effects
Goal: An oral anticoagulant that is not affected by diet and does not require routine monitoring

First attempt: ximelagatran, an oral direct anti-IIa (thrombin) inhibitor

Result: failure due to liver toxicity

Next try: dabigatran another oral direct anti-IIa (thrombin) inhibitor

Result: approved for use in 2010 for stroke prevention in non-valvular atrial fibrillation (NVAF)

Now there are 4 other FDA approved direct oral anticoagulants (DOACs): rivaroxaban, apixaban, edoxaban and betrixaban, all targeting factor Xa
Targets for anticoagulation and laboratory testing

Contact factors

APTT

XII

XI

IX

VIII

VII

V

X

II

I

PT/INR

RVVT

Anti-Xa
(Test + FXa DOAC targets)

dTT, ecarin methods

Anti-IIa (thrombin) drug targets

Monomer, fibrinogen and thrombin time test

D-dimer, FDP

Clot formation

Clot lysis
Simplified Definition of Terms

Venous thromboembolism or VTE: clots within the deep venous system, also known as deep vein thrombosis (or DVT) and pulmonary embolism (or PE)

Pharmacokinetics (PK): drug concentration after administration

Pharmacodynamics (PD): the drug effect after administration

Peak levels: the maximum drug concentration after administration

Trough levels: the drug level just before the next drug dose

Therapeutic range: the recommended target drug effect, usually either a concentration or test effect (e.g. INR and warfarin therapy).
Oral anticoagulants: Compare and Contrast

• Mechanism of action:
  • Warfarin – vitamin K antagonist, takes days to reach therapeutic range
  • DOACs – direct factor inhibitor, takes several hours to reach desired level.

• Dose:
  • Warfarin – variable doses based on desire therapeutic target
  • DOACs – fixed doses based on indication (renal adjustment)

• Monitoring:
  • Warfarin requires frequent and episodic monitoring to assure maintenance in the desired therapeutic range
  • DOACs typically does not require frequent or episodic monitoring

• Dietary effect:
  • Warfarin dosing predicated based on daily vitamin K intake (e.g. greens)
  • DOAC dosing not affected by diet, although rivaroxaban and betrixaban are taken with food to increase absorption.

• Decreased risk for serious hemorrhage with DOACs as compared to warfarin
Dabigatran etexilate: Pradaxa® (Boehringer Ingelheim) is an oral direct thrombin inhibitor, immediate acting

Binds free and bound thrombin (factor IIa)

Bioavailability: ~ 3 – 7%

80% renally excreted

Peak concentration: 1.5 – 3.0 hrs after ingestion

Half-life: ~13 hours
Dabigatran – FDA approved indications

Stroke prevention in NVAF

Treatment of Deep vein Thrombosis (DVT) or pulmonary embolism (PE)

Secondary prevention of venous thromboembolism (VTE)

Thromboprophylaxis after knee or hip surgery
Rivaroxaban

Rivaroxaban: Xarelto® (Janssen Bayer) is an oral direct factor Xa inhibitor, immediate acting

Inhibits both free and bound factor Xa

Bioavailability is between 80 – 100%

Primarily renally excreted (~70%)

Peak concentration about 2-3 hours after ingestion, increased absorption is noted with food intake

Half-life is approximately 2 – 13 hours and dependent on renal function
Rivaroxaban – FDA approved Indications

- Stroke prevention in NVAF
- Treatment of DVT or PE
- Secondary prevention of VTE
- Thromboprophylaxis after knee or hip surgery
Apixaban

Apixaban: Eliquis® (Bristol Myers Squibb) is an oral direct factor Xa inhibitor, immediate acting

Inhibits both free and bound factor Xa

Bioavailability is ~50%

Clearance primarily through feces

Peak concentration about 3 - 4 hours after ingestion.

Half-life is approximately ~12 hours
Apixaban – FDA approved Indications

Stroke prevention in NVAF

Treatment of DVT or PE

Secondary prevention of VTE

Thromboprophylaxis after knee or hip surgery
Edoxaban: Savaysa (Daiichi Sankyo) is an oral direct factor Xa inhibitor, immediate acting

Inhibits both free and bound factor Xa

Bioavailability is ~60%

Clearance approximately 50% via the kidneys

Peak concentration about 1 – 2 hours after ingestion.

Half-life is approximately ~12 hours
Edoxaban – FDA approved Indications

Stroke prevention in NVAF

Treatment of DVT or PE
Betrixaban

Betrixaban: Bevyxxa (Portola Pharmaceuticals) is an oral direct factor Xa inhibitor that is only FDA approved for VTE prophylaxis in acutely medically ill hospitalized patients, immediate acting. Should be take with food.

Inhibits both free and bound factor Xa

Bioavailability is ~35%

Clearance primarily through feces

Peak concentration about 3 – 4 hours after ingestion.

Half-life is approximately ~20 hours
Summary

• There are currently 5 FDA approved DOACs for clinical use as an alternative to warfarin for long term anticoagulation

• DOACs are currently approved for adult use only, but numerous pediatric trials are underway
  • Additional adult clinical trials for DOAC use in cancer patients

• The performance characteristics of each DOAC and their effect on laboratory testing will be explored in future sessions.
References

5. Food and Drug Administration. Bevyxxa—Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl.pdf.
Disclosures/Potential Conflicts of Interest

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