Drug-Drug Interactions of Non-Vitamin K Antagonist Oral Anticoagulants (NOACs): How to Manage?

Naglaa Bazan, PhD
Fellow and Head of Clinical Pharmacy
Critical Care Medicine Department
Cairo University Hospitals

Outline

• History and large scale clinical trials of NOACs
• Advantages and clinical challenges of NOACs
• Drug-Drug Interactions of NOACs and their management
• Evidence of clinical significance of Drug-Drug Interactions of NOACs
Non-Vitamin K Antagonist Oral Anticoagulants (NOAC)

2010  **Dabigatran**  *(Direct thrombin inhibitor)*  **Pradaxa**

2011  **Rivaroxaban**  *(Factor Xa inhibitor)*  **Xarelto**

2012  **Apixaban**  *(Factor Xa inhibitor)*  **Eliquis**

2015  **Edoxaban**  *(Factor Xa inhibitor)*  **Savaysa®, Lixiana®**

Four Randomised Controlled Trials

- **Dabigatran**
- **Rivaroxaban**
- **Apixaban**
- **Edoxaban**
Advantages of NOACs

- Lack for monitoring
- Fixed-dose regimens
- Predictable pharmacokinetic profile
- Short Half lives and quicker onset of action
- Fewer food and drug interactions

Kocabas U. et al. IJCAC; 2016. 2(4): 167-173

Non-Vitamin K Antagonist Oral Anticoagulants (NOACs)

Vitamin K antagonists (VKA)
Clinical Challenges of New Oral Anticoagulants

Drug-Drug Interactions
Adherence
Monitoring
Reversal

Drug-Interactions

Drug-Drug Interactions
Drug-Nutrient Interactions
Drug-Dietary Supplement Interactions
Drug-Drug interactions

- Desired
- Reduced
- Unwanted effects

Types of Drug-Drug interactions

- Pharmacokinetic Interactions
  - One drug affects the other’s absorption, distribution, metabolism, or excretion

- Pharmacodynamic Interactions
  - Interactions in which drugs influence each other’s effects directly
Pharmacokinetic Drug-Drug Interactions of NOACs

Main Pharmacokinetic Interactions of New Oral Anticoagulants

P-gp
One of the drug transporters that determine the uptake and efflux of a range of drugs
In the gut, P-glycoprotein pumps drugs back into the lumen, decreasing their absorption
All NOACs

CYP3A4
Many, but not all, of the drugs which are transported by P-glycoprotein are also metabolised by CYP3A4
Inducers and inhibitors can affect serum drug concentrations
All NOACs except Dabigatran
Main Pharmacokinetic Interactions of New Oral Anticoagulants

**Dabigatran Etexilate**

- It is a prodrug which becomes active via hydrolysis following oral absorption

**Elimination**
- Primarily renally eliminated (80%)
- Half life=12-17 hrs

**Metabolism**
- It is a substrate of the p-glycoprotein transport system (P-gp)
Drug-Drug Interactions of Dabigatran

Renal + Pharmacodynamic

Antiplatelet, NSAIDs, and antithrombotic effects can increase bleeding risk


Stangier J. Clin Pharmacokinet 2008; 47:285-95
Pradaxa prescribing information. Boehringer-Ingelheim, 2016

U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

* = Adjust dose CrCl = 30-50 ml/min
* = Avoid use at CrCl = 15-30 ml/min
* = Avoid use
Rivaroxaban

- **Elimination**
  - one-third is eliminated via the kidneys unchanged (66%)
  - The remaining as inactive metabolites after hepatic transformation
  - Half life=5-9 hrs ((9–13 h in the elderly)

- **Metabolism**
  - Cytochrome P-450 system (CYP) and includes both the 3A4, and 2J2 families of enzymes
  - P-glycoprotein, adenosine triphosphate–binding cassette G2 (ABCG2) efflux transporter protein, which is expressed in the liver and kidneys

---

**Drug-drug interactions of Rivaroxaban**

- Renal
- CYP3A4
- P-gp

- Antiplatelet, NSAIDs and antithrombotic effects can increase bleeding risk


### U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

#### CYP3A4 Inhibitors
- amiodarone
- clarithromycin
- cyclosporine
- indinavir
- itraconazole
- ketoconazole
- nefazodone
- ritonavir
- saquinavir
- telaprevir
- vardenafil
- verapamil
- voriconazole
- zafirlukast

#### CYP3A4 Inducers
- amiloride
- dalfopristin
- fosamprenavir
- miconazole
- nelfinavir
- nefazodone
- oral contraceptives
- ritonavir
- telithromycin

### U.S. Food and Drug Administration, Drug Development and Drug Interactions: Table of Substrates, Inhibitors, and Inducers

#### Combined Strong P-glycoprotein AND CYP3A4 Inhibitors
- amiodarone
- clarithromycin
- cyclosporine
- indinavir
- itraconazole
- ketoconazole

#### Combined Strong P-glycoprotein AND CYP3A4 Inducers
- barbiturates
- carbamazepine
- dexamethasone
- phenytoin
- rifampin
- St John's wort

---

**Notice:**

- The combination of certain drugs may lead to adverse interactions. Please consult a healthcare professional for advice.
Apixaban

- **Elimination**
  - Less renal excretion than rivaroxaban (27%)  
  - Half life=10-14 hrs

- **Metabolism**
  - Substrate for CYP3A4, P-glycoprotein ABCG2 transporter proteins

---

**Drug-drug interactions of Apixaban**


_Eliquis prescribing information. Bristol-Myers Squibb, Pfizer 2016_
Edoxaban

- **Elimination**
  - Renal excretion (50%)
  - Do not use edoxaban in patients with CrCl >95 ml/min in the US
  - Half life=9-11 hrs

- **Metabolism**
  - Substrate for both CYP3A4 and P-glycoprotein
Drug-Drug interactions of Edoxaban

Renal

CYP3A4

P-gp

Antiplatelet, NSAIDs and antithrombotic effects can increase bleeding risk


Savaysa prescribing information. Daiichi-Sankyo, 2015

Drug-Drug Interactions of Edoxaban

Dual P-gp/CYP3A4 inhibitors

No dose adjustment or use 30 mg once daily

Dual P-gp/CYP3A4 inducers

Avoid concomitant use of rifampin
Drug Absorption: Food

Dabigatran: Take with or without food
Rivaroxiban: 10 mg, take with or without food; 15 mg, 20 mg with food (Enhances bioavailability)
Apixaban: Take with or without food
Edoxaban: Take with or without food

Drug-Drug Interactions of NOACs

Trikha R et al. Cardiology 2017;136:115–124
Clinical Significance of New Oral anticoagulants Drug-drug Interactions

Effect of Ketoconazole and Diltiazem on the Pharmacokinetics of Apixaban,

Apixaban+ Ketokonazole (Cmax > 62%)
Apixaban+Diltiazem (Cmax > 31%)

Frost CE et al., BJCP 2014
Apixaban with Antiplatelet Therapy After ACS

A case of fatal pulmonary embolism may be related to sub-therapeutic levels of rivaroxaban, through the interaction of rifampicin with rivaroxaban

Drug Interaction Management of Warfarin Versus New Oral Anticoagulants

Warfarin
- Many reported drug interactions
- Much published literature and clinical expertise to guide management
- INR monitoring
- Warfarin dose adjustment

New Oral Anticoagulants
- Few reported drug interactions
- Little published literature or clinical expertise to guide management
- No established laboratory monitoring method
- NOAC dose adjustment

Conclusion

- Pharmacokinetic drug-drug interactions that may occur in association with the new oral anticoagulants are largely mediated by the P-gp efflux transporter protein alone (dabigatran etexilate) or in combination with CYP3A4 enzymes
- In addition to managing pharmacokinetic-based interactions, clinicians should avoid unnecessary pharmacodynamics interactions between the newer oral Anticoagulants and antiplatelet agents (eg, ASA, clopidogrel) and NSAIDs (eg, naproxen)
- Drug-drug interactions of NOACs are more significant in patients with renal impairment
Conclusion

• **Praxbind** (IDARUCIZUMAB) is humanized monoclonal antibody fragment (Fab) which is an antidote for dabigatran and there are ongoing clinical trials of antidotes for direct factor Xa inhibitors

• Real-world data investigating the clinical significance of drug-drug interactions of NOACs is needed

• Importance of anticoagulation specialist/ clinical pharmacist involvement in patient education and follow-up

References


References


References

- Kocabas U, a, Kaya E, Acer G. Novel oral anticoagulants in non-valvular atrial fibrillation: Pharmacological properties, clinical trials guideline recommendations, new antidote drugs and real-world data. IJCAC; 2016. 2(4): 167-173
• Drug Interactions of New Oral Anticoagulants Exist…How do we manage them?