بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

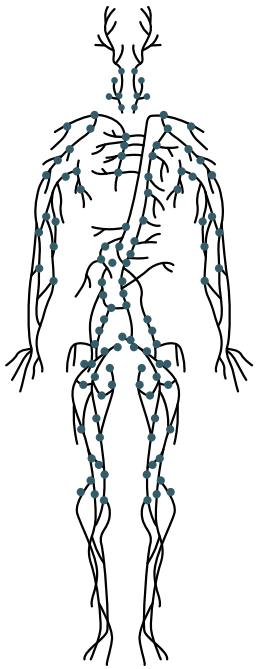
ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

FINAL | Lecture 3 (Pt.1)

Dabigatran (Pradaxa)

Written by:
Qusai Al-Shannag

Reviewed by:
Qusai Al-Shannag



An overview:

In previous lectures, the doctor discussed heparin and warfarin, noting that warfarin is associated with numerous problems and is a common cause of patient hospitalizations due to adverse effects. Unfractionated heparin was described as being used in cases of deep vein thrombosis (DVT), pulmonary embolism, and following hip or knee replacement surgery, and is administered intravenously. More recently (after 2004), newer anticoagulant agents, known as new oral anticoagulants (NOACs), have been introduced. These agents are classified into two groups: those that inhibit factor IIa (thrombin) and those that inhibit factor Xa.

Dabigatran

سبحان الله وبحمده سبحان الله العظيم

- MOA: direct thrombin inhibitor which inhibits:
  - Both free and fibrin-bound thrombin
  - Cleavage of fibrinogen to fibrin
  - Thrombin-induced platelet aggregation

Dabigatran

- Monitoring
  - PPT
- Onset: 1 hour, delayed by food
- Antidote: None
- ADRs
  - Bleeding (8% to 33%; major ≤ 6%)
  - Dyspepsia (11%)

Although activated partial thromboplastin time (aPTT) can be used to monitor therapy, routine monitoring is generally unnecessary because dabigatran is administered as a homogeneous oral formulation with predictable pharmacokinetics and a consistent anticoagulant effect. However, in cases where bleeding occurs as an adverse effect, aPTT may be assessed since it serves as a monitoring parameter for thrombin (factor IIa)–related anticoagulants.

In clinical practice, we monitor the extent of bleeding rather than the drug effect, as dabigatran exerts a direct and dose-dependent anticoagulant action, resulting in a predictable response.

The onset of action occurs within approximately one hour. Unlike warfarin, dabigatran does not require bridging therapy and is not associated with the risk of transient thrombosis during initiation.

The incidence of major bleeding with dabigatran is comparable to that of warfarin; however, dabigatran is more frequently associated with gastrointestinal bleeding and dyspepsia.

Dabigatran

Note: Drug-drug interactions with dabigatran are less frequent compared to warfarin.

- Drug interactions
  - **Category X**: P-Gp inducers
  - **Category D**: Amiodarone, P-Gp inhibitors, quinidine, St. john's Wort, verapamil

Dabigatran is a substrate of P-glycoprotein (P-Gp), a transport protein located in the gastrointestinal tract that functions to expel substances and drugs from enterocytes back into the intestinal lumen. Consequently, when dabigatran is administered concurrently with a P-Gp inducer, its absorption decreases, leading to subtherapeutic levels and an increased risk of thrombosis. Conversely, co-administration with a P-Gp inhibitor enhances dabigatran absorption, raising plasma concentrations and increasing the risk of bleeding. Therefore, careful attention is required when prescribing these combinations, as dabigatran has a narrow therapeutic index.

Common side effect

- The most of dabigatran is gastrointestinal upset.

- When compared with people anticoagulated with warfarin, patients taking dabigatran had fewer life-threatening bleeds, fewer minor and major bleeds, including intracranial bleeds, but the rate of gastrointestinal bleeding was significantly higher.

- Dabigatran capsules contain tartaric acid, which lowers the gastric pH and is required for adequate absorption. The lower pH has previously been associated with dyspepsia; some hypothesize that this plays a role in the increased risk of gastrointestinal bleeding.

- If a small amount of GI bleeding is diagnosed, the clinicians may consider adding 12 receptor inhibitor (H,RA), proton pump inhibitors (PPls)

- **Oesophagitis**

- Antidote ➔ **idarucizumab**

اللهم صل على محمد وعلى آله وصحبه أجمعين

Further explanation:

- The gastrointestinal discomfort associated with dabigatran is primarily due to its formulation, which contains tartaric acid. Tartaric acid is included to ensure consistent absorption of dabigatran, as it helps maintain an acidic environment necessary for optimal drug dissolution and bioavailability. However, this acidic component can irritate the gastrointestinal mucosa, potentially leading to esophagitis (reported in approximately 20% of patients) and contributing to the risk of gastrointestinal bleeding by further lowering the gastric pH.

- In cases of significant bleeding, the specific antidote idarucizumab, a monoclonal antibody fragment that neutralizes dabigatran's anticoagulant effect, is administered.

Contraindication

1. active pathological bleeding

2. The use of dabigatran should also be avoided in patients with mechanical prosthetic heart valves due to the increased risk of thromboembolic events (e.g. valve thrombosis, stroke, and myocardial infarction) and major bleeding when compared with warfarin. Current FDA guidelines states that patients with mechanical heart valves should not be using dabigatran.

Clinical trials have shown unexpected findings with dabigatran use in patients with prosthetic heart valves. Unlike warfarin, where the target INR is adjusted to 2.5–3.5 rather than 2–3 for such patients, dabigatran was associated with increased thromboembolic events and higher rates of major bleeding compared with warfarin. **The exact reason for this outcome remains unclear.** Consequently, dabigatran is contraindicated in patients with mechanical heart valves, and heparin or warfarin remain the preferred anticoagulants in these cases. This emphasizes that anticoagulant selection must be individualized — understanding when to use warfarin, heparin, dabigatran, or enoxaparin is essential, as each has specific indications and limitations, , and a narrow therapeutic index.

Factor Xa inhibitor (rivaroxaban, apixaban)

- Dosing recommendations do not recommend administering rivaroxaban with drugs known to be strong combined CYP3A4/P-glycoprotein inhibitors because this results in significantly higher plasma concentrations of rivaroxaban.

- Spinal anesthesia or puncture, people who are being treated with anti- thrombotic agents are at higher risk for developing a hematoma, long-term or permanent paralysis

- Antidote Andexanet

لا إله إلا أنت سبحانك إني كنت من الظالمين

Further explanation:

- Factor Xa inhibitors such as rivaroxaban and apixaban have comparable anticoagulant activity to warfarin and can serve as effective alternatives, except in patients with prosthetic heart valves, where they are contraindicated, similar to dabigatran. These agents are approved for atrial fibrillation, deep vein thrombosis, post-stroke prevention, and prophylaxis after hip and knee replacement surgery. Their antidote is Andexanet, though it is very new and expensive (approximately 1500 JD per dose).
- Rivaroxaban is contraindicated with CYP3A4 and P-glycoprotein inhibitors, as it is metabolized by CYP3A4 and expelled by P-Gp.
- Factor Xa inhibitor have a bleeding risk comparable to warfarin.
- In surgical settings, patients taking rivaroxaban or apixaban (particularly apixaban) are typically avoided for spinal anesthesia, even if the drugs are stopped before the procedure, due to the high risk of spinal hematoma, which can result in permanent or long-term paralysis.

Another topic introduced in previous lecture (HIT):

- In the case of heparin-induced thrombocytopenia (HIT), patients develop widespread thrombosis that requires urgent anticoagulant treatment. Warfarin should never be administered during the acute phase, as initiating warfarin within the first two days can exacerbate the thrombotic situation and increase the risk of further clot formation. Similarly, if the patient is receiving unfractionated heparin, fractionated (low-molecular-weight) heparin should not be given, as it can worsen HIT.
- Alternative anticoagulants include dabigatran, rivaroxaban, or apixaban, but these are administered orally and therefore have a delayed onset, which may be insufficient in life threatening situations and the patient could die before their onset. The preferred treatment is an intravenous, non-heparin anticoagulant such as fondaparinux, which directly inhibits factor IIa (thrombin) activity, (ChatGPT said fondaparinux inhibits factor Xa not IIa). Other options exist but are not commonly required and may be discussed in later lectures.

QUIZ

PHARMACOLOGY

LECTURE 3A

السودان لا بواكي له...

اللهم فرج عن أهلنا في السودان والفاشر وأنزل عليهم شآبيب رحمتك وأطعمهم من جوع وآمنهم من خوف، اللهم انتقم من الدعم السريع ومن وقف في ظهرهم، وفرج عن أهلنا المستضعفين في غزة وفي الإيغور وفي شتى بقاع المسلمين، وارفع عنا إثم الخذلان وأعنا على نصرتهم.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			