International Conference on
Contemporary Technological Solutions towards fulfillment of Social Needs

Anticoagulants: A Review on Pharmacology, Dose and Uses

Sandeep Sahu [1], Dr. Narendra Kumar Lariya [2],
[1,2]Vedica College of Pharmacy,
RKDF University, Bhopal, India

Abstract: Historically, most patients who required parenteral anticoagulation received heparin, whereas those patients requiring oral anticoagulation received warfarin. Due to the narrow therapeutic index and need for frequent laboratory monitoring associated with warfarin, there has been a desire to develop newer, more effective anticoagulants. Consequently, in recent years many novel anticoagulants have been developed.

The emergency physician may institute anticoagulation therapy in the short term (e.g. heparin) for a patient being admitted, or may start a novel anticoagulation for a patient being discharged. Similarly, a patient on a novel anticoagulant may present to the emergency department due to a hemorrhagic complication. Consequently, the emergency physician should be familiar with the newer and older anticoagulants. This review emphasizes the indication, mechanism of action, adverse effects, and potential reversal strategies for various anticoagulants that the emergency physician will likely encounter.

Keywords: Thrombosis, Coagulation, Anticoagulants, Unfractionated Heparin, Low Molecular Weight Heparins, Direct Thrombin Inhibitors, Warfarin, Dabigatran, Rivaroxaban, Apixaban

I Introduction

During routine homeostatic conditions, the human body maintains a constant balance between thrombus formation and destruction. This equilibrium is maintained by a complex interaction between platelets and the vascular endothelium, the coagulation cascade, and the fibrinolytic system. The coagulation cascade (Figure 1) involves an interaction between the contact activation pathway (previously called the intrinsic system), and the tissue factor pathway (previously the extrinsic system) [1]. These two seemingly independent pathways lead to the conversion of factor X to Xa, which is the start of the common pathway. This common pathway converts prothrombin to thrombin, which subsequently catalyzes the formation of fibrin and ultimately leads to the stabilization of aggregated platelets to form a stable clot.1,2

Historically, vitamin K antagonists, such as warfarin, were the only anticoagulants widely available for human use. It has been estimated that more than 65,000 patients are treated in U.S. emergency departments (ED) annually for warfarin-related hemorrhage. Because of this high rate of bleeding, along with the drug's narrow therapeutic index and the need for frequent monitoring, there has been a desire to create safer anticoagulants without such strict drug monitoring [2]. Consequently, there have been several novel anticoagulants (NACs) developed, including direct thrombin inhibitors (e.g. dabigatran), and factor Xa inhibitors (e.g. rivaroxaban, apixaban), designed to target different points of the coagulation cascade (Figure 2).

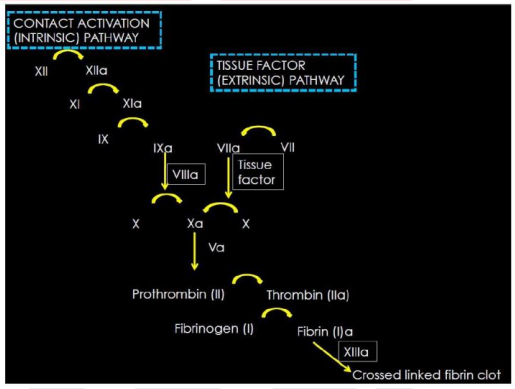

Figure 1: The Coagulation Cascade

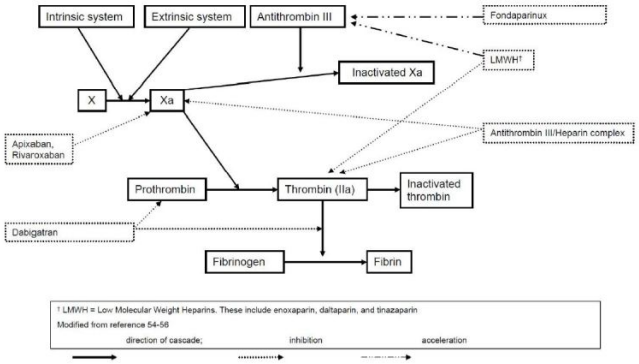

Figure 2: Different Points of The Coagulation Cascade

Classification of anti coagulants

- Anticoagulants used in vivo parentally
  - Heparin
  - Low molecular weight heparins
  - Heparinoids
- Anticoagulants used in vivo orally

  - Coumarin derivative
  - Indandion derivative

- Anticoagulants used in vitro
  - Heparin
  - Calcium complexing agents

II List of Anticoagulants

2.1 Oral Anticoagulants

1. **Apixaban:** Apixaban (Eliquis) is an oral anticoagulant medicine that is used for the prevention of blood clots and prevention of stroke. Apixaban works by preventing your blood from clotting quickly or as effectively as normal [3].
   Mechanism of Action: It does this by blocking a substance in your blood that is involved in the development of blood clots, called factor Xa. Apixaban does not require monitoring with regular blood tests although you may still require a blood test to check kidney and liver function is satisfactory before starting treatment and at least once a year thereafter.
   Uses: Apixaban as mainly used for the prevention of venous thromboembolism in adults after elective hip or knee surgery.

2. **Dabigatran:** Dabigatran etexilate (Pradaxa) is a type of oral anticoagulant medicine that is used for the prevention of blood clots and prevention of stroke.
   Mechanism of Action: Dabigatran is a direct thrombin inhibitor – a type of medicine that lowers the chance of blood clots forming in your body by blocking thrombin, the blood's central clotting agent.
   Uses: It can be used to prevent blood clots from forming in veins and arteries in the legs, lungs, brain or heart. Dabigatran does not require monitoring with regular blood tests although it will still require a blood test to check that your kidneys are working properly (renal function) as the medication is removed (excreted) from the body through the kidneys.

3. **Edoxaban:** Edoxaban (Lixiana EU) is an oral anticoagulant medicine that is used for the prevention of blood clots and prevention of stroke. Edoxaban is licensed in the UK for patients diagnosed with non-valvular atrial fibrillation (not caused by heart valve problems).
   Mechanism of Action: Edoxaban is an anticoagulant that directly inhibits factor Xa, which is a key component in the formation of blood clots.
   Uses: Edoxaban to be used to prevent stroke and systemic embolism in people with non-alvular atrial fibrillation and for treating and for preventing deep vein thrombosis and pulmonary embolism.

4. **Rivaroxaban:** Rivaroxaban (Xarelto) is an oral anticoagulation medicine that is used to prevent blood clots following hip or knee surgery, for treatment and prevention of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) and as a possible treatment to prevent stroke and blood clots embolism for people with non-valvular atrial fibrillation (not caused by heart valve problems).
   Mechanism of Action: Rivaroxaban works by preventing your blood from clotting quickly or as effectively as normal. It does this by blocking a substance in your blood that is involved in the development of blood clots, called factor Xa.
   Uses: Rivaroxaban as an option for prevention of venous thromboembolism in adults having elective total hip or total knee replacement surgery.

5. **Warfarin:** Warfarin is an oral anticoagulant medicine that is used to prevent and treat blood clots. It is a Vitamin K antagonist [4].
   Mechanism of Action: The blood needs vitamin K to be able to clot and warfarin slows the production of vitamin K in the body which increases the time it takes for your blood to clot [5].

2.2 Low Molecular Weight Heparin and Heparin

LMWHs have increased bioavailability after subcutaneous injection, renal clearance that is dose-independent, and a longer half-life ($17-21\ h$) when compared to UFH. LMWHs are administered in fixed doses for thromboprophylaxis, or in total body weight adjusted doses for therapeutic anticoagulation.

1. **Heparin** Heparins are an injectable anticoagulant that is used to treat or to prevent blood clots. Low molecular weight heparin (LMWH) and standard unfractionated heparin are two types of heparin commonly used as anticoagulants to treat blood clotting, and given as a preventative treatment when patients have had certain types of surgery. It is also used to treat and prevent cancer associated thrombosis [6].

   LMWH is usually given as a subcutaneous injection and can normally be administered by the individual or their carer/healthcare professional without the need for hospitalisation and monitoring.

2. **Enoxaparin** Enoxaparin sodium is an anticoagulant medication (blood thinner). It is used to treat and prevent deep vein thrombosis (DVT) and pulmonary embolism (PE) including during pregnancy and following certain types of surgery. It is also used in those with acute coronary syndrome (ACS) and heart attacks. It is given by injection just under the skin or into a vein. Other uses include inside kidney dialysis machines [7, 8].

Common side effects include bleeding, fever, and swelling of the legs. Bleeding may be serious especially in those who are undergoing a spinal tap. Use during pregnancy appears to be safe for the baby. Enoxaparin is in the low molecular weight heparin family of medications.

Enoxaparin was first made in 1981 and approved for medical use in 1993. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.

Enoxaparin binds to and potentiates antithrombin (a circulating anticoagulant) to form a complex that irreversibly inactivates clotting factor Xa. It has less activity against factor IIa (thrombin) compared to unfractionated heparin (UFH) due to its low molecular weight.

3. **Fondaparinux** Fondaparinux (trade name Arixtra) is an anticoagulant medication chemically related to low molecular weight heparins [9]. Clinically, it is used for the prevention of deep vein thrombosis in patients who have had orthopedic surgery as well as for the treatment of deep vein thrombosis and pulmonary embolism.

   Fondaparinux is similar to enoxaparin in reducing the risk of ischemic events at nine days, but it substantially reduces major bleeding and improves long-term mortality and morbidity. It has been investigated for use in conjunction with streptokinase. Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor [10–12]. Fondaparinux binds antithrombin and accelerates its inhibition of factor Xa. Apart from the O-methyl group at the reducing end of the molecule, the identity and sequence of the five monomeric sugar units contained in fondaparinux is identical to a sequence of five monomeric sugar units that can be isolated after either chemical or enzymatic cleavage of the polymeric glycosaminoglycans heparin and heparin sulfate (HS) [13].

   Within heparin and heparin sulfate this monomeric sequence is thought to form the high-affinity binding site for the anti-coagulant factor antithrombin (AT). Binding of heparin or HS to AT has been shown to increase the anti-coagulant activity of antithrombin 1000 fold. In contrast to heparin, fondaparinux does not inhibit thrombin [14].

4. **Dalteparin** Dalteparin is a low molecular weight heparin. Like other low molecular weight heparins, dalteparin is used for prophylaxis or treatment of deep vein thrombosis and pulmonary embolism. It is normally administered by self-injection. The CLOT study, published in 2003, showed that in patients with malignancy and acute venous thromboembolism, dalteparin was more effective than warfarin in reducing the risk of recurrent embolic events. Dalteparin is not superior to unfractionated heparin in preventing blood clots [15].

   Heparins are cleared by the kidneys, but studies have shown that dalteparin does not accumulate even if kidney function is reduced.

III Conclusion

Acute hemorrhage is the most feared adverse event associated with all anticoagulants. While it is relatively uncommon that patients present with a life-threatening hemorrhage while on systemic anticoaguation, prompt recognition and management is vital. As the NAC become more frequently used in clinical settings, it will be imperative that the emergency physician has a thorough understanding of these agents, and is knowledgeable about potential reversal strategies, when available.

REFERENCES

[1] A. P. Wheeler and T. W. Rice, "Coagulopathy in critically iii patients: Part 2 — soluble clotting factors and hemostatic testing," *Chest*, vol. 137, no. 1, pp. 185–194, 2010. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0012369210600323

[2] B. Dahlbäck, "Blood coagulation," *The Lancet*, vol. 355, no. 9215, pp. 1627–1632, 2000. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S014067360002225X

[3] L. Friberg, "Safety of apixaban in combination with dronedarone in patients with atrial fibrillation," *International Journal of Cardiology*, vol. 264, pp. 85–90, 2018. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0167527318305114

[4] S. N, S. LS, K. SR, and B. DS, "National estimates of emergency department visits for hemorrhage-related adverse events from clopidogrel plus aspirin and from warfarin," *Archives of Internal Medicine*, vol. 170, no. 21, pp. 1926–1933, 2010. [Online]. Available: http://dx.doi.org/10.1001/archinternmed.2010.407

[5] J. Hirsh, M. O'Donnell, and J. W. Eikelboom, "Beyond unfractionated heparin and warfarin: current and future advances," *Circulation*, vol. 116, no. 5, pp. 552–60, Jul 2007. [Online]. Available: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.106.685974

[6] M. K. Roberts and S. Chaney, "Heparin-induced thrombocytopenia," *The Journal for Nurse Practitioners*, vol. 14, no. 5, pp. 402 – 408.e3, 2018. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1555415518302265

[7] Q. X. Ng, C. Seng, C. Y. X. Ho, and W.-S. Yeo, "Enoxaparin: A cause of postoperative fever?" *Medical Hypotheses*, vol. 121, pp. 47–48, 2018. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0306987718308880

[8] D. Masic, A. Cook, T. Cober, A. Joshi, and M. Liebo, "Effect of enoxaparin on bleeding and thrombosis in patients supported with ventricular assist devices," *Journal of Cardiac Failure*, vol. 24, no. 8, Supplement, p. S28, 2018. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S1071916418304421

[9] K. Harter, M. Levine, and S. Henderson, "Anticoagulation drug therapy: A review," *The western journal of emergency medicine*, vol. 16, pp. 11–17, 01 2015. [Online]. Available: https://dx.doi.org/10.5811%2Fwestjem.2014.12.22933

[10] Y. Ding, C. V. V. Prasad, H. Bai, and B. Wang, "Efficient and practical synthesis of fondaparinux," *Bioorganic & Medicinal Chemistry Letters*, vol. 27, no. 11, pp. 2424–2427, 2017. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0960894X17303785

[11] Z. C. Lum, R. A. Monzon, J. Bosque, S. Coleman, G. C. Pereira, and P. E. D. Cesare, "Effects of fondaparinux on wound drainage after total hip and knee arthroplasty," *Journal of Orthopaedics*, vol. 15, no. 2, pp. 388–390, 2018. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0972978X18300771

[12] R. Pesavento, M. Amitrano, J. Trujillo-Santos, P. D. Micco, S. Mangiacapra, L. López-Jiménez, C. Falgá, F. García-Bragado, C. Piovella, P. Prandoni, and M. Monreal, "Fondaparinux in the initial and long-term treatment of venous thromboembolism," *Thrombosis Research*, vol. 135, no. 2, pp. 311–317, 2015. [Online]. Available: http://www.sciencedirect.com/science/article/pii/S0049384814006665

[13] D. S. Budnitz, M. C. Lovegrove, N. Shehab, and C. L. Richards, "Emergency hospitalizations for adverse drug events in older americans," *New England Journal of Medicine*, vol. 365, no. 21, pp. 2002–2012, 2011, pMID: 22111719. [Online]. Available: https://doi.org/10.1056/NEJMsa1103053

[14] S. M. Weitz JI, Eikelboom JW, "Antithrombotic therapy and prevention of thrombosis," *American College of Chest Physicians evidence-based clinical practice guidelines. Chest*, vol. 141, no. 2, 2012.

[15] M. G. Papich, "Dalteparin," in *Saunders Handbook of Veterinary Drugs (Fourth Edition)*, fourth edition ed., M. G. Papich, Ed. St. Louis: W.B. Saunders, 2016, pp. 201 – 202. [Online]. Available: http://www.sciencedirect.com/science/article/pii/B9780323244855001856