CPQ Medicine (2019) 6:3
Review Article

An Overview of Anticoagulants

Mohammad Shoaib Hamrah[1*], Mohammad Hassan Hamrah[2,6], Mohammad Hussain Hamrah[3,6], Ahmad Edris Hamrah[5], Toba Dahi[4], Mohammad Naim Musammen[5] & Mohammad Hashem Hamrah[6]

[1]*Center for Rural Health, School of Health Sciences, University of Tasmania*

[2]*Faculty of Stomatology, Kunduz University, Kunduz, Afghanistan*

[3]*Arya University Faculty of Medicine, Mazar-i-Sharif, Afghanistan*

[4]*Faculty of Dentistry, AbantIzzet Baysal University, Bolu, Turkey*

[5]*Faryab Public Health Department*

[6]*Dr. Mohammad Hashem Hamrah's Curative Clinic*

[*]**Correspondence to:** Dr. Mohammad Shoaib Hamrah, Center for Rural Health, School of Health Sciences, University of Tasmania.

Copyright

Received: 18 March 2019
Published: 15 April 2019

Keywords: *Anticoagulants; Thrombin Inhibitors; Vitamin K*

Abstract

Anticoagulant therapy remains the mainstay of medical therapy and prevention of venous thromboembolic disease for many years. Traditional anticoagulants have many limitations, such as unpredictable pharmacologic and pharmacokinetic responses and various adverse effects including serious bleeding complications. Strict laboratory control is also required for the use of traditional anticoagulants in terms of both insufficient and excessive dosage. Recently, several new oral anticoagulants have been developed and are expected to replace older agents with their ease of use

and more favorable pharmacodynamic profiles. The main adverse effect of all anticoagulants is hemorrhage. Therefore, it is a crucial point for clinicians to have a better understanding of anticoagulant pharmacology, dosing, and toxicity.

Introduction

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism (PE). VTE is a leading cause of death and disability worldwide [1]. It is the third predominate causes of cardiovascular deaths, followed by acute coronary syndrome and stroke [2]. Treatment of VTE involves the same measures as prevention and treatment of acute events and its complications, which are post thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension [3,4].

Anticoagulants are the cornerstone therapy for thrombosis prevention and treatment, and are commonly employed, although their use is often associated with adverse drug reactions and increased readmission rates. Eldery patients will present to emergency departments with adverse reactions to Warfarin and it is estimated that 50 percent of cases require hospitalization [5].

Since 2008, new oral anticoagulants non-vitamin K antagonist oral anticoagulants (NOAC) can be used as alternatives to warfarin in carefully selected patients [6]. The NOACs do not require routine blood testing for international normalized ratio (INR) monitoring blood monitoring or dose adjustment. They can be given in fixed doses and, have much fewer drug interactions, and have a rapid onset and offset of action with a wide therapeutic window [7]. They offer attractive alternatives to and were developed to overcome limitations associated with warfarin and heparin products. However, rivaroxaban has been associated with serious thrombotic events while dabigatran has been associated with serious bleeding [8]. There are risks associated with the use of anticoagulants, and an understanding of the risks and benefits of anticoagulant therapy is important. This review summarizes the traditional anticoagulants and new anticoagulants in routine clinical practice.

Anticoagulants generally include, heparins (Unfractionated Heparin and Low-molecular-weight heparin), Intravenous thrombin inhibitors, Fondaparinux, Oral vitamin K antagonist and New anticoagulants (Direct thrombin inhibitors and Factor Xa inhibitors).

1. Unfractionated Heparin

Intravenous (IV) and subcutaneous (SC) are two most frequently used injection routes in Unfractionated Heparin (UFH) [9]. Optimal dosing of subcutaneous UFH for therapeutic anticoagulation need to be large enough (>30,000 U/day) to overcome UFHs low bioavailability. However, IV administration of UFH rapidly achieves therapeutic plasma concentrations that can be effectively monitored and adjusted based on infusion rates [10]. UFH's elimination from the systemic circulation is dose-related and occurs through two independent mechanisms [11]. The initial phase is the rapid and saturable binding to endothelial cells, macrophages, and local proteins where UFH is depolymerized. The second phase is a slower, non-saturable, renal-mediated clearance [12]. UFH clearance from systemic circulation is dose related, and UFH is cleared

primarily via depolymerization, the higher molecular weight chains being cleared more rapidly than lower weight counterparts [13]. The clinical efficacy of UFH varies greatly from person to person due to its interactions with a number of plasma proteins and the endothelium. The activated partial thromboplastin time (aPTT) is used to measure the anticoagulant effect of UFH and adjust the dose to maintain levels in the target therapeutic range. The aPTT reflects the ability of the heparin antithrombin complex to inhibit thrombin, factor Xa, and other coagulation enzymes in the intrinsic coagulation pathway. There are some advantages of the test including its relative inexpensiveness, wide availability, simple performance, and rapid results [14]. This test should be measured initially, and the infusion rate adjusted every 6h. Once a steady dosage schedule has been established, the frequency of monitoring can be extended [11,15].

The different dosing nomograms have been proposed for treatment of thromboembolic disease, however, the standard of practice for administering heparin currently is to employ a weight-based nomogram. This method assures that patients will promptly achieve adequate levels of anticoagulation, thus decreasing the likelihood of recurrent venous thromboembolism without extra bleeding-risk [16].

2. Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is a class of anticoagulant medications that do not require monitoring for an appropriate therapeutic effect to be achieved. These compounds are breakdown products of UFH through chemical or enzymatic depolymerization, generating fragments with molecular weights between 1000 and 10,000 Daltons [17]. LMWHs preferentially inhibit factor X than thrombin [18]. LMWH binds less to plasma proteins than UFH [19]. Therefore, LMWHs have more predictable anticoagulant activity than UFH as well as the dosing is more predictable, and their effects are more selective thus, they are associated with a lower bleeding risk. Laboratory monitoring is usually not necessary when dosage is based on body weight. They are more resistant to neutralization by platelet factor 4 than UFH and have less inhibitory effect on platelet function [20]. LMWHs are usually administered subcutaneously once or twice daily. LMWH can also be administered in smaller doses for the primary prevention of DVT. LMWHs are contraindicated in the context of advanced renal. In most patients, LMWH does not require the laboratory monitoring. If monitoring is necessary, anti-factor Xa levels must be measured because most LMWH preparations have little effect on aPTT [17].

3. Intravenous Thrombin Inhibitors

Lepirudin and desirudin are derivatives of hirudin [21]. Lepirudin is indicated for the treatment of thrombosis complicating heparin-induced thrombocytopenia. It is given as an intravenous infusion with or without a bolus. Since lepirudin is excreted by the kidneys, dose adjustments are required in patients with renal impairment [18]. The aPTT is required to monitor their effects during treatment. Anaphylaxis can also occur if patients with hirudin-induced antibodies are re-exposed to hirudin [22].

4. Fondaparinux

Fondaparinux is a synthetic analogue of heparin, and it given subcutaneously. It also has predictable absorption and degree of anticoagulation. Fondaparinux has been efficacious and as safe as heparin for the

treatment of DVT (deep vein thrombosis) or pulmonary emboli, respectively [23]. It is contraindicated in patients with a creatinine clearance below 30mL/min and for VTE (venous thromboembolism) prophylaxis in patients weighing less than 50kg [24].

5. Oral Vitamin K Antagonist

Coumarin derivatives, such as warfarin, acenocoumarol and phenprocoumon are frequently prescribed oral anticoagulants to treat and prevent thromboembolism [25]. The coagulation factors (II, VII, IX, and X) of anticoagulant proteins (C and S) require carboxylation, by converting glutamic acid to gamma-carboxyglutamic acid, for their normal functions. The carboxylation procedure requires KH_2 [26]. Warfarin blocks the regeneration of vitamin K1 epoxide and in doing, so also the synthesis of vitamin K dependent clotting factors, which include Factors II, VII, IX and X, and the anticoagulant proteins C and S. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K dependent clotting factors. The vitamin promotes the biosynthesis of gamma-carboxyglutamic acid residues in these proteins which are essential for biological activity [27]. Warfarin produces an anticoagulant effect by diet, concurrent drugs, and genetic polymorphisms [28]. It is believed that dietary vitamin K intake could counteract the anticoagulant effect by warfarin. A large amount of vitamin K causes warfarin resistance for up to a week [29]. Bleeding is the most important complication of warfarin, and the yearly incidence of bleeding at a rate of 13 per 100 patients [30]. The risk of bleeding attributed to warfarin is related both to the degree of anticoagulation, patient-related factors and the concurrent use of antiplatelet agents or other drugs [31]. The daily maintenance doses are 0.5mg/day and 15mg/day. The typical maintenance dose is about 4.5mg/day, although this is lower in the elderly [32]. Reversal therapy with prothrombin complex concentrate, vitamin K, fresh frozen plasma or recombinant factor VIIa [33]. The aim of anticoagulant therapy with warfarin is to maintain the target INR (the therapeutic INR range is 2.0 to 3.0). The warfarin dose adjustments needs to be made for persistently out of range INR values. Warfarin is indicated for the prevention and treatment of venous thrombosis and its extension and the prevention and treatment of the thromboembolic complications associated with atrial fibrillation. Warfarin is also used to prevent recurrent transient ischemic attacks and to reduce the risk of recurrent myocardial infarction [34]. Unfractionated heparin or LMWH may be used for patients with a high risk of thromboembolism as a bridge until a therapeutic dose of unfractionated heparin or LMWH is achieved [35].

6. New Anticoagulants

Newer anticoagulants approved or undergoing clinical studies. This class of anticoagulants offer superior therapeutic control over coagulations with minimal bleeding complications [36].

A. Direct Thrombin Inhibitors

Thrombin converts fibrinogen to fibrin, which forms the basis of the cross-linked blood clot. It activates factors XI, VIII, and V at or near the activated platelet, stimulating platelets and generating more thrombin. By activating XIII, it also accelerates the formation of cross-linked fibrins and clot stabilization. In addition to its procoagulant role, thrombin plays a role in growth factor synthesis, cell proliferation, prostaglandin I2 synthesis, and chemotaxis of polymorphonuclear cells [37]. Direct thrombin inhibitors (DTIs) bind directly

to thrombin and blocks its interaction with its substrates without interfering with the platelet hemostatic role [21]. DTIs block thrombin by two ways; bivalent DTIs block simultaneously the active site and exosite 1 and act as competitive inhibitors of fibrin [38]. Therefore, DTIs can inhibit both free and fibrin-bound thrombin. There are also other advantages such as more predictable anticoagulant effects due to the absence of interaction with plasma proteins, not being neutralized by PF4, the inhibition of thrombin-induced platelet aggregation and absence of immune-mediated thrombocytopenia [39]. Univalent DTIs (argatroban, ximelagatran, and dabigatran exteilate) non-covalently and reversibly bind to thrombin, leaving a small fraction of free thrombin [21]. Recombinant hirudins, argatroban, which is a parenteral DTI, but is metabolized by the liver. These drugs have a reversible and selective binding to thrombin. As a result, minimal risk of bleeding and rapid restoration of hemostasis to baseline upon discontinuation of these class of medications [40]. Ximelagatran is the first orally available DTI, which demonstrates a new era of anticoagulation for the prevention and treatment of VTE, however, this drug pretested hepatotoxic side effects. As a result, it was withdrawn from the market due to a risk of significant hepatotoxicity. Intestinally, Ximelagatran has shown improved antithrombotic efficacy when compared with traditional anticoagulation therapies [41]. Dabigatran etexilate was developed to overcome the limited oral bioavailability of dabigatran; drug interactions [42].

B. Factor Xa Inhibitors

Factor Xa is a crucial site of amplification in the coagulation process, generating approximately 1,000 thrombin molecules from a single Xa molecule [43]. Prothrombin is physiologically activated by the prothrombinase complex (factor Xa, factor Va, phospholipids, and calcium). The conversion of fibrinogen to fibrin, the basic building block of all blood clots, is then catalyzed by thrombin. The rate of prothrombin activation by factor Xa in a prothrombinase complex is dramatically increased, whereas heparin inhibits factor Xa and thrombin to a similar degree, LMWHs have a relatively greater inhibitory effect against factor Xa, which has drawn attention as a potential anticoagulant target [9]. Direct factor Xa inhibitors is a potent and selective direct inhibitor of factor Xa without affecting platelet aggregation [44]. They are attributed to a decrease in the incidence of rebound thrombosis than direct and indirect thrombin inhibitors [45]. Despite the benefits of oral factor Xa inhibitors, there were a high incidence of major and clinically relevant bleeding including gastrointestinal bleeding [46].

Conclusions

Anticoagulants are the cornerstone therapy for the treatment and prevention of thrombosis. Vitamin K antagonists such as warfarin have been the mainstay of anticoagulation therapy for more than half a century. Over the past few years, direct oral anticoagulants have developed which include one direct thrombin inhibitor (dabigatran etexilate) and three factor Xa inhibitors (apixaban, edoxaban and rivaroxaban). Since there is no need for invasive monitoring with new oral anticoagulants, the main complication of these drugs are bleeding, especially gastrointestinal bleeding.

Acknowledgements

This study was supported by the Terumo Foundation for Life Science and Art.

Bibliography

1. Yan, C., Wang, X., Su, H. & Ying, K. (2017). Recent progress in research on the pathogenesis of pulmonary thromboembolism: An old story with new perspectives. *Bio Med Research International., 2017*(6516791), 1-10.

2. Piazza, G. & Goldhaber, S. Z. (2010). Venous thromboembolism and atherothrombosis an integrated approach. *Circulation, 121*(19), 2146-2150.

3. Kahn, S. R. & Ginsberg, J. S. (2004). Relationship between deep venous thrombosis and the postthrombotic syndrome. *Arch Intern Med., 164*(1), 17-26.

4. Wilkens, H., Lang, I., Behr, J., Berghaus, T., Grohe, C., Guth, S., *et al.* (2011). Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol., 154* Suppl 1, S54-S60.

5. Budnitz, D. S., Lovegrove, M. C., Shehab, N. & Richards, C. L. (2011). Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med., 365*(21), 2002-2012.

6. Oktay, E. (2015). Will NOACs become the new standard of care in anticoagulation therapy? *International Journal of the Cardiovascular Academy, 1*(1), 1-4.

7. Mekaj, Y. H., Mekaj, A. Y., Duci, S. B. & Miftari, E. I. (2015). New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. *Ther Clin Risk Manag., 11,* 967-977.

8. Alquwaizani, M., Buckley, L., Adams, C. & Fanikos, J. (2013). Anticoagulants: a review of the pharmacology, dosing, and complications. *Current Emergency and Hospital Medicine Reports, 1*(2), 83-97.

9. Garcia, D. A., Baglin, T. P., Weitz, J. I. & Samama, M. M. (2012). Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 141*(2), e24S-e43S.

10. Weitz, D. S. & Weitz, J. I. (2010). Update on heparin: what do we need to know? *J Thromb Thrombolysis., 29*(2), 199-207.

11. Bussey, H., Francis, J. L. & Group, H. C. (2004). Heparin overview and issues. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 24*(8P2), 103S-107S.

12. Irwin, R. S. & Rippe, J. M. (2008). Irwin and Rippe's intensive care medicine: Lippincott Williams & Wilkins.

13. Nutescu, E. A., Burnett, A., Fanikos, J., Spinler, S. & Wittkowsky, A. (2016). Erratum to: pharmacology of anticoagulants used in the treatment of venous thromboembolism. *J Thromb Thrombolysis., 42*(2), 296-311.

14. Lee, M. S., Menon, V., Schappert, J., Wilentz, J. R., Singh, V. & Hochman, J. S. (2004). Establishing a new target range for unfractionated heparin for acute coronary syndromes. *J Thromb Thrombolysis., 17*(2), 121-126.

15. Raschke, R. A., Reilly, B. M., Guidry, J. R., Fontana, J. R. & Srinivas, S. (1993). The weight-based heparin dosing nomogram compared with a standard care nomogram: a randomized controlled trial. *Ann Intern Med., 119*(9), 874-881.

16. Bernardi, E., Piccioli, A., Oliboni, G., Zuin, R., Girolami, A. & Prandoni, P. (2000). Nomograms for the administration of unfractionated heparin in the initial treatment of acute thromboembolism-an overview. *Thromb Haemost, 84*(1), 22-26.

17. Borris, L. C. (2010). Venous thromboembolic disease after total hip arthroplasty. *Minerva Ortopedica E Traumatologica., 61*(2), 145-154.

18. Hirsh, J., Bauer, K. A., Donati, M. B., Gould, M., Samama, M. M. & Weitz, J. I. (2008). Parenteral anticoagulants: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 133*(6 Suppl), 141S-159S.

19. Young, E., Cosmi, B., Weitz, J. & Hirsh, J. (1993). Comparison of the non-specific binding of unfractionated heparin and low molecular weight heparin (Enoxaparin) to plasma proteins. *Thromb Haemost., 70*(4), 625-630.

20. Malloy, R. J., Rimsans, J., Rhoten, M., Sylvester, K. & Fanikos, J. (2018). *Unfractionated Heparin and Low-Molecular-Weight Heparin.* In: Anticoagulation Therapy. edn.: Springer, 31-57.

21. Marcello Di Nisio, M., Middeldorp, S. & Büller, H. R. (2005). Direct Thrombin Inhibitors. *N Engl J Med., 353*(10), 1028-1040.

22. Greinacher, A. & Warkentin, T. E. (2008) The direct thrombin inhibitor hirudin. *Thromb Haemost, 99*(5), 819-829.

23. Büller, H. R., Davidson, B. L., Decousus, H., Gallus, A., Gent M, *et al.* (2004). Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med., 140*(11), 867-873.

24. Smythe, M. A., Dager, W. E. & Patel, N. M. (2004). Managing complications of anticoagulant therapy. *J Pharm Pract., 17*(5), 327-346.

25. Wessler, S. & Gitel, S. N. (1986). Pharmacology of heparin and warfarin. *J Am Coll Cardiol., 8*(6 Suppl B), 10B-20B.

26. Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M. & Palareti, G. (2012). Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest, 141*(2 Suppl), e44S-e88S.

27. Deaton, J. G. & Bhimji, S. S. (2017). *Toxicity, Warfarin.* In: StatPearls [Internet]. edn.: StatPearls Publishing; 2017.

28. Hirsh, J., Fuster, V., Ansell, J. & Halperin, J. L. (2003). American Heart Association/American College of Cardiology foundation guide to warfarin therapy. *J Am Coll Cardiol., 107*(12), 1692-1711.

29. Lurie, Y., Loebstein, R., Kurnik, D., Almog, S. & Halkin, H. (2010). Warfarin and vitamin K intake in the era of pharmacogenetics. *Br J Clin Pharmacol., 70*(2), 164-170.

30. Linkins, L-A, Choi, P. T. & Douketis, J. D. (2003). Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med., 139*(11), 893-900.

31. Fitzmaurice, D. A., Blann, A. D. & Lip, G. Y. (2002). Bleeding risks of antithrombotic therapy. *BMJ., 325*(7368), 828-831.

32. Gallus, A. S., Baker, R.I., Chong, B. H. & Ockelford, P. A. (2000). Consensus guidelines for warfarin therapy. *The Medical Journal of Australia, 172*(12), 600-605.

33. Tran, H. A., Chunilal, S. D., Harper, P. L., Tran, H., Wood, E. M. & Gallus, A. S. (2013). An update of consensus guidelines for warfarin reversal. *Med J Aust., 198*(4), 198-199.

34. Hirsh, J., Dalen, J. E., Anderson, D. R., Poller, L., Bussey, H., Ansell J, Deykin, D. & Brandt, J. T. (1998). Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest, 114*(5 Suppl), 445S-469S.

35. Wigle, P. & Hein, B., Bloomfield, H. E., Tubb, M. & Doherty, M. (2013). Updated guidelines on outpatient anticoagulation. *Am Fam Physician., 87*(8), 556-566.

36. Meschia, J. F., Bushnell, C., Boden-Albala, B., Braun, L. T., Bravata, D. M., Chaturvedi, S., *et al.* (2014). Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke, 45*(12), 3754-3832.

37. Coughlin, S. R. (1994). Thrombin receptor function and cardiovascular disease. *Trends Cardiovasc Med., 4*(2), 77-83.

38. Bates, S. & Weitz, J. (2000). The mechanism of action of thrombin inhibitors. *The Journal of Invasive Cardiology, 12* Suppl F, 27F-32.

39. Lee, C. J. & Ansell, J. E. (2011). Direct thrombin inhibitors. *Br J Clin Pharmacol., 72*(4), 581-592.

40. Koster, A., Fischer, K. G., Harder, S. & Mertzlufft, F. (2007). The direct thrombin inhibitor argatroban: a review of its use in patients with and without HIT. *Biologics: Targets & Therapy, 1*(2), 105-112.

41. Evans, H. C., Perry, C. M. & Faulas, D. (2004). Ximelagatran/melagatran. *Drugs, 64*(6), 649-678.

42. Stangier, J. & Clemens, A. (2009). Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost., 15*(suppl 1), 9S-16S.

43. Mann, K. G., Brummel, K. & Butenas, S. (2003). What is all that thrombin for. *Thromb Haemost, 1*(7), 1504-1514.

44. Rupprecht, H. J. & Blank, R. (2010). Clinical pharmacology of direct and indirect factor Xa inhibitors. *Drugs, 70*(16), 2153-2170.

45. Perzborn, E., Roehrig, S., Straub, A., Kubitza, D. & Misselwitz, F. (2011). The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. *Nature Reviews Drug Discovery, 10*(1), 61-75.

46. Connolly, G. & Spyropoulos, A. C. (2013). Practical issues, limitations, and periprocedural management of the NOAC's. *J Thromb Thrombolysis., 36*(2), 212-222.