Chapter 5
Drugs for Thromboprophylaxis: Unfractionated Heparin, Low Molecular Weight Heparin, Warfarin, and Fondaparinux

José Aguirre and Alain Borgeat

Abstract The world of antithrombotic prophylaxis is a revolutionary phase due to the introduction of numerous new compounds in the daily practice. However, traditional antithrombotics are still in use. This chapter deals with advantages and disadvantages of the traditional drugs used in this context: unfractionated heparin, low molecular weight heparin, and fondaparinux. The use of these drugs will decrease, but specific indications will remain. This point will also be emphasized in this chapter.

Keywords Antithrombotic drugs • Unfractionated heparin • Low molecular weight heparin • Warfarin • Fondaparinux • Deep venous thrombosis • Pulmonary embolism

Introduction

The most widely available, approved, and currently used anticoagulants are unfractionated heparin (UFH), low molecular weight heparins (LMWHs) (e.g., enoxaparin, tinzaparin, dalteparin), vitamin K antagonists (VKA) (e.g., warfarin), and fondaparinux [1–3].

UFH has been discovered as animal-derived extractive drug in 1916 by Jay McLean at John Hopkins in Baltimore and has been available for nearly a century. Karl Paul Link discovered in 1940 coumarin as a substance contained in sweet clover hay which killed cattle by bleeding [4]. From the 1980s to the late 1990s, the evolution of UFH

J. Aguirre, M.D. • A. Borgeat, M.D. (✉)
Division of Anesthesiology, Balgrist University Hospital,
Forchstrasse 340, 8008 Zürich, Switzerland
e-mail: alain.borgeat@balgrist.ch

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toward the chemically fractionated low molecular weight heparins and after further fractionating toward fondaparinux which contains the essential pentasaccharide anticoagulant structure shared by both UFH and LMWHs took place [4].

Patients undergoing major orthopedic surgery are subjected to the risk of venous thromboembolism (VTE), consisting in deep venous thrombosis (DVT) and pulmonary embolism (PE), independently of the choice of anesthesia. Without thromboprophylaxis, 40–60 % of patients will develop DVT, and 10 % of those will suffer a PE [5, 6]. After total hip arthroplasty and total knee arthroplasty, the prevalences of total DVT and PE are 41–85 % and ≤30 %, respectively [7–10]. Actually, the incidence of fatal PE is 0.1–0.2 with 480,000 VTE-related deaths estimated to occur annually in the EU [11].

Prophylaxis with coumarins has been the gold standard for VTE prevention after acute coronary syndrome for over 60 years. However, this treatment requires frequent monitoring for dose adjustment, and multiple interactions with other drugs are the major drawbacks of this drug. In the 1970s, VTE prevention after major surgery was started with heparins reducing postoperative VTE-related mortality to 5 %. Due to the need for aPTT monitoring for dosage adjustment, low molecular weight heparins (LMWH) were introduced 10 years later. Fondaparinux was the next development to hit the market, an effective and safe indirect factor-Xa inhibitor which is used parenterally [12].

The Use of Anticoagulants and Neuraxial Anesthesia

Neuraxial anesthesia bears the risk of spinal/epidural hematoma (SEH) with possible compression in the spinal canal, potentially resulting in neuroplegia if not recognized and treated early. The risk of SEH is about 1:150,000 but increases by 15-fold with the use of anticoagulant therapy without appropriate precautions [5]. This risk is further increased if indwelling epidural catheters are used. This requires a proper management of anticoagulated patients, particularly with the continuing development of new and possibly more potent anticoagulants. The risk of hematoma associated with a specific anticoagulant is difficult to estimate, and prospective randomized trials are not possible [13–15]. Therefore, a rigid strategy to balance the risk of hematoma with effective thromboprophylaxis is needed. Several national guidelines have been published, most of them based on case reports or pharmacokinetic properties of the most used agents, leading to drug-specific recommendations [5, 16]. Patient management focuses on the timing of needle/catheter placement and catheter removal according to the timing of anticoagulant drug administration. The goal is to perform these manipulations when the drug concentration is at its lowest [13–15]. Another strategy is to delay the initiation of postsurgical anticoagulation to further reduce the risk of hematoma [5]. However, the risk of hematoma is increased with concomitant use of medications such as nonsteroidal anti-inflammatory drugs or other anticoagulants, further complicating patient management. Therefore, all patients undergoing neuraxial anesthesia must be monitored for clinical signs of

neurologic impairment to assure prompt intervention to avoid irreversible neurological complications [13–15].

Unfractionated Heparin

The anticoagulant action of UFH derives from the binding to antithrombin and catalyzing the inactivation of factors IIa, Xa, IXa, and, also if to a lesser extent, also from XIa and XIIa [5]. UFH binds to a number of plasma proteins of endothelial cells, macrophages, and platelet factor 4. This widespread binding leads to a low bioavailability and clinically unpredictable pharmacokinetic and pharmacodynamic properties. Moreover, it has also been associated with the occurrence of heparin-induced thrombocytopenia (HIT). UFH was clinically used from the 1970s onward and was the first anticoagulant to be used for the prevention and treatment of DVT and PE.

UFH has a short half-life (2–4 h) and a quick onset; therefore, they are considered to be safe and well controllable for thromboembolic prophylaxis and acute treatment of thrombosis. UFH has a number of limitations such as parenteral administration and possible development of life-threatening heparin-induced thrombocytopenia (HIT) type II (Table 5.1) [20, 21]. UFH requires laboratory monitoring, dosage adjustment, and potentially monitoring for HIT [22]. Due to its considerable intra- and interindividual variability, therapy with UFH is unpredictable and inappropriate for long-term use. One important advantage compared to LMWH is the possibility to neutralize its effect by protamine sulfate (Tables 5.2 and 5.3).

Unfractionated Heparin and Neuraxial Anesthesia

The consensus statement from the American Society of Regional Anesthesia and Pain Medicine (ASRA) on regional anesthesia in the anticoagulated patient bases its recommendations for UFH on the first recommendations more than 20 years ago which were supported by reviews of case series and case reports of postpuncture spinal hematoma [13–15]. ASRA recommends that UFH administration be delayed for 1 h after needle placement. Indwelling neuraxial catheters should be removed 2–4 h after the last UFH dose, and the next dose can be given 1 h after catheter removal. Notwithstanding, patients must be carefully monitored for any clinical signs of spinal hematoma [13–15].

Low Molecular Weight Heparin

LMWHs (e.g., enoxaparin, tinzaparin, dalteparin) are derived from UFH by enzymatic or chemical depolymerization and have therefore shorter heparin chains. This leads to a better bioavailability and therefore better predictability of effect without

Table 5.1 Advantages and disadvantages of anticoagulant therapy with warfarin, unfractionated heparin, low molecular weight heparin, and fondaparinux [17–19]

Anticoagulant	Advantages	Disadvantages
Warfarin	Gold standard for primary and secondary prophylaxis of venous thromboembolism	Frequent monitoring
	Oral administration	Slow onset and offset of action
	Can be antagonized with vitamin K	Drug and dietary interactions
		Narrow therapeutic window
		Risk of bleeding complications
UFH	Fast acting	Frequent monitoring
	High efficacy	Parenteral administration
	Fine regulation of dosage steps	Indirect action: needs antithrombin
	Antagonization with protamine sulfate	Potential of severe heparin-induced thrombocytopenia
		Nonspecific protein binding with unpredictable response
		Variable bioavailability
		Risk of bleeding complications
		Risk of osteoporosis
LMWH	Variable dosage: once or twice daily	Subcutaneous injection
	High efficacy	Indirect action: needs antithrombin
	No monitoring needed (if no renal insufficiency)	Risk of thrombocytopenia
		Risk of osteoporosis
		Bleeding complications (in patients with renal insufficiency)
Fondaparinux	Once-daily dose	Subcutaneous injection
	Does not affect thrombin activity	Indirect action: needs antithrombin
	Inhibits free factor Xa	
	Low risk of induced thrombocytopenia	
	No monitoring needed if no renal insufficiency	

the need for routine monitoring, if there is no renal insufficiency. In this case and due to half-life prolongation, monitoring and dose reduction are recommended [22]. LMWH also binds to antithrombin and shows a selective inhibitory effect on factor Xa [22]. LMWH has greater inhibitory activity against factor Xa than thrombin (IIa), and the protein binding of these agents is less than that of UFH. Consequently, the risk of HIT is therefore lower, and the anticoagulation is more predictable compared to UFH. LMHW is contraindicated in patients with a creatinine clearance of <30 ml/min. The longer half-life of LMWH (2–6 h after single sc injection) allows different dosage regimens: once daily for thromboembolic prophylaxis or twice daily for treatment of thrombosis [23].

LMWHs have overcome some of the limitations of UFH such as a more predictable anticoagulant with no need for routine coagulation monitoring. The need for subcutaneous administration has some limits in the use for the outpatient setting.

Table 5.2 Comparison of advantages or disadvantages of different anticoagulants and their clinical implications

Advantage or disadvantage of anticoagulants	Clinical implications
LMWH vs. UFH	
+ Increased bioavailability	Subcutaneous dosage possible
+ Inferior binding to plasma proteins	Predictable anticoagulant response, no monitoring needed
+ Inferior binding to platelet factor 4	Reduced risk of induced thrombocytopenia
+ Inferior binding to endothelium	Increased half-life with possible once-daily dosage
+ Inferior binding to bone cells	Reduced risk of osteoporosis
– Protamine sulfate as antidote less effective	Reduced reversal possibility after overdose or bleeding
Fondaparinux vs. LMHW	
+ Higher safety	No biological contamination, reduced risk of osteoporosis and of induced thrombocytopenia
+ Defined, single target (factor Xa)	Reduced vulnerability to interactions
– Inhibition of factor Xa less potent than heparin	Increased risk of thrombosis in acute coronary syndrome without the concomitant administration of heparin
– No antidote	Reduced reversal possibility after overdose or bleeding
Vitamin K antagonists vs. LMWH and fondaparinux	
+ Oral administration	Ideal for outpatient setting
+ Vitamin K as antidote	Reversal possible in case of overdose or bleeding
– Longer plasma half-life	Reduced reversal onset in case of overdose or bleeding
– Interaction with drugs, food, and genetic polymorphisms	Close laboratory monitoring and dose adjustment

UFH unfractionated heparin, *LMWH* low molecular weight heparin

In summary, the advantages of LMWH over UFH are higher availability and longer half-life, which allow once-daily subcutaneous administration, more predictable anticoagulant responses that obviate the need of laboratory monitoring (for dosage tailoring), and less binding to platelet factor 4 and bone cells that results in a lower risk for thrombocytopenia and osteoporosis (Tables 5.2 and 5.3).

LMWH and Neuraxial Anesthesia

- *Preoperative LMWH*: ASRA recommends that needle placement should occur at least 10–12 h after the last dose of LMWH [13–15]. However, most European guidelines recommend a delay of at least 12 h, but a delay of 20 h is recommended by French guidelines [5]. ASRA further recommends that needle placement occurs at least 24 h after the last dose if a higher dose of LMWH is used

Table 5.3 Pharmacokinetic and pharmacodynamic characteristics of traditional and newer anticoagulants

	UFH	LMWH	Warfarin	Fondaparinux
Target	Factor Xa and thrombin	Factor Xa and thrombin	Vitamin K-dependent factors and inhibitors	Factor Xa
Source	Biological	Biological	Synthetic	Synthetic
Administration	IV/sc	Sc	Oral	Sc
Bioavailability	30 %	90 %	90 %	100 %
Half-life	1 h	4 h	15–44 h	17 h
Antidote	Protamine sulfate	Protamine sulfate	Vitamin K/FFP/PCC	No
Thrombocytopenia	<5 %	<1 %	No	?

FFP fresh frozen plasma, *PTCC* prothrombin complex concentrates, *IV* intravenous, *Sc* subcutaneous

(e.g., 1 mg/kg enoxaparin every 12 h or 1.5 mg/kg daily) [13–15]. Neuraxial techniques should be avoided in patients administered LMWH 2 h preoperatively due to coincidence with peak anticoagulant activity [13–15].

- *Postoperative LMWH*: Postoperative LMWH application is based on the dosing regimen chosen. Twice-daily administration might be associated with an increased risk of spinal hematoma [13–15]. The ASRA guidelines recommend that the first dose be administered at earliest 24 h postoperatively, independently of anesthetic technique, and only in the presence of correct surgical hemostasis. Indwelling catheters should be removed if indicated before initiation of LMWH therapy. In the case of epidural catheter, the indwelling catheter may be left overnight and removed the following day, with the first dose of LMWH administered at least 2 h after catheter removal [13–15]. If given once daily, the first postoperative LMWH dose should be administered 6–8 h postoperatively, and the second postoperative dose should occur not before 24 h after the first dose. Indwelling neuraxial catheters may be safely maintained, but the catheter should be removed 10–12 h after the last dose of LMWH. A further dose might be given 2 h after catheter removal. However, European guidelines recommend in this context a 4–6-h delay [5].

Vitamin K Antagonists

Long-term anticoagulation is still performed with VKA. Warfarin is the most frequently used. VKA interferes with the metabolism of vitamin K by influencing the posttranslational carboxylation of coagulation factors II, VII, IX, and X and other coagulation proteins such as proteins C, S, and Z, leading to a reduced coagulant effect by abolishing their potential to be activated on phospholipid surfaces after calcium-dependent binding [24]. The benefits of warfarin therapy in a wide range of patients with thromboembolic complications are well established. Hart et al. described in a meta-analysis of trials involving 2,900 patients that dose-adjusted

warfarin reduced the relative risk of stroke by 62 % compared with placebo in patients with atrial fibrillation [25]. Nevertheless, warfarin has unpredictable pharmacodynamic, pharmacokinetic, and pharmacogenetic properties, causing major variability in patients' dose responses [24]. However, warfarin's use is hampered by numerous limitations like its narrow therapeutic window, its need for frequent coagulation monitoring and dose adjustments, dietary restrictions, bleeding risk, its delayed onset and offset of action, and frequent interactions with other drugs [26]. These problems lead to adverse effects, which might be responsible for additional hospitalizations (see Table 5.3) [27]. At the beginning, VKA therapy requires frequent therapeutic monitoring and dose adjustments using the international normalized ratio (INR), based on the prothrombin time (PT) [24]. Administration of vitamin K is recommended to reverse a mildly increased INR. In the case of life-threatening bleeding or intracranial hemorrhage, prothrombin complex concentrates are recommended [24, 28]. If prothrombin complex concentrates are not available, fresh frozen plasma is still used. Off-label use of recombinant factor VIIa has also been reported to reverse the INR effect [29].

VKA and Neuraxial Anesthesia

The anesthetic management of patients receiving warfarin for long-term therapy or as perioperative thromboembolic prophylaxis is controversially discussed. The ASRA consensus statement bases its recommendations mainly on case reports of spinal hematoma, drug pharmacology, and on the clinical relevance of vitamin K coagulation factor levels [13–15]. For patients requiring long-term anticoagulation, VKA therapy should be stopped 4–5 days before surgery, and the INR should be measured before initiation of neuraxial block. For patients receiving a prophylactic dose of warfarin more than 24 h before surgery, INR measurements should be checked before neuraxial anesthesia. Neuraxial catheters can only be removed when the INR is less than 1.5 [13–15]. This value has been derived from studies that correlate hemostasis with clotting actor activity levels greater than 40 %.

Fondaparinux

Fondaparinux is approved since 2001, meanwhile with a broad spectrum of indications comparable to that of enoxaparin, including thromboembolic prophylaxis, treatment of venous thrombosis, pulmonary embolism, and unstable angina pectoris [30]. Fondaparinux was the first synthetic substance interfering with the factor Xa with some advantages over the LMWH (Tables 5.1 and 5.2). It further reduces the low molecular heparin structure to the essential pentasaccharide structure which is responsible for binding to antithrombin. The pentasaccharide binds like UFH and LMWH to antithrombin, producing a conformational change at the reactive site of

antithrombin resulting in reversible binding to factor Xa with 700-fold higher affinity compared to heparins. This leads to a selective inhibition of factor Xa by mechanisms identical to LMWHs but without affecting the thrombin activity [22]. Only free factor Xa, but not factor Xa bound to the prothrombinase complex, is inhibited by fondaparinux [31]. Like all heparins, it is dependent on the presence and functionality of antithrombin. Fondaparinux catalyzes factor Xa inhibition by antithrombin but has no effect on the rate of thrombin inactivation. A meta-analysis by Turpie et al. showed that fondaparinux has greater efficacy in VTE prevention than LMWH [32]. Fondaparinux is eliminated via the renal route and is contraindicated in patients whose creatinine clearance is <30 ml/min. Fondaparinux is administered subcutaneously and has a longer half-life (14–21 h) than LMWHs allowing for single-daily dosing, with the first dose administered 6 h postoperatively [22] (Table 5.2). The risk of HIT is relatively low [33]. Fondaparinux does not require routine coagulation monitoring [34], except in patient with renal dysfunction [31, 35]. There are no clinically available reversal agents for fondaparinux, although partial reversal has recently been described with recombinant factor VIIa [33]. Fondaparinux is 100 % bioavailable and has a highly predictable pharmacokinetic profile.

The benefit-to-risk ratio of fondaparinux in preventing VTE was investigated in four randomized phase II trials in patients undergoing surgery for hip fracture, hip replacement, and major knee surgery. A meta-analysis of these trials demonstrated that fondaparinux reduced the incidence of venographically proven venous thromboembolism by 55.2 % compared with enoxaparin. The superior profile of fondaparinux over enoxaparin could also be demonstrated for proximal DVT with a reduction of 57.4 % [30]. Fondaparinux was also investigated for the initial treatment of venous thromboembolism in the MATISSE DVT trial [36] and the MATISSE PE [37] trials suggesting that fondaparinux is as effective and safe as UFH or LMWH for the initial treatment of patients with pulmonary embolism or deep vein thrombosis, respectively.

Fondaparinux and Neuraxial Anesthesia

Rosencher et al. recommend that fondaparinux to be started between 6 and 8 h after end of surgery [5]. Indwelling epidural catheters should not be removed until 36 h (or at least two half-lives) after the previous dose. The next dose should not be given until 12 h after catheter removal. The 48-h window required between two injections of fondaparinux is achieved by omitting one injection. In the EXPERT (*evaluation of Arixtra for the prevention of venous thromboembolism in daily practice*) study, this regimen was associated with safe catheter removal without affecting thromboprophylaxis efficacy. In patients receiving 2.5 mg fondaparinux daily for 3–5 weeks after major orthopedic surgery, the rate of symptomatic VTE was similar in patients with and without catheters. Moreover, no neuraxial hematoma was reported [38]. Although the risk of spinal hematoma is still unknown, spinal hematoma has been associated with the use of fondaparinux [13–15]. Therefore, close monitoring for

clinical signs of neurological deterioration of patients receiving fondaparinux with neuraxial anesthesia and the need for postoperative indwelling epidural catheters are mandatory [5, 13–15].

Clinical Use of UFH, LMWH, Warfarin, and Fondaparinux

These anticoagulants have been successfully used in several clinical conditions caused by arterial and venous thromboembolism. The most important and clinically relevant are primary prophylaxis of VTE (DVT and PE) especially in high-risk orthopedic surgery patients and in different medical conditions, like the treatment and secondary prophylaxis of acute venous thromboembolism; prevention stroke in atrial fibrillation; and treatment of acute coronary syndromes [39].

UFH and LMWHs reduce venous thromboembolic complications by 60 % after hip and knee arthroplasties and in high-risk medical conditions including heart failure, prolonged immobilization in bed, etc. A further clinical field is their use in addition to dual antiplatelet therapy with aspirin and clopidogrel in acute coronary syndromes. Vitamin K antagonists reduce by >90 % the recurrence of venous thromboembolism and by 60 % cardioembolic stroke due to atrial fibrillation [24].

Fondaparinux is not only equally safe but also at least as effective as UFH and LMWH for the initial treatment of venous thromboembolism after once-daily subcutaneous injection [40, 41].

A limitation of UFH, LMWHs, and fondaparinux is the need of parenteral or subcutaneous administration which may complicate their use in the outpatient setting [22]. Oral VKA like warfarin and related compounds offers a clear advantage in the management of outpatients. On the other hand, they need regular laboratory monitoring with INR and frequent dosage tailoring due to many interactions with other drugs [24]. Despite the development of a standardized method to express the prothrombin time results (the international standardized ratio (INR)) with a substantial improvement in safety and efficacy, clinical use of vitamin K antagonists is still unsatisfactory mainly because many elderly patients do not have the autonomy to attend monitoring facilities at regular intervals.

The accuracy of UFH laboratory monitoring for the required dose adjustment is lagging behind that of VKA, as there is no result standardization obtained by different laboratory tests and reagents (activated clotting time, activated partial thromboplastin time). Therefore, the introduction of LMWHs, which only need dosage adjustment based upon patient weight in the absence of renal insufficiency, was a decisive step forward in patient management [42]. The introduction of fondaparinux was another improvement as this drug can be administered at a fixed dose of 2.5 mg sc without adjustment to body weight if patients have a renal function with a clearance <30 ml/min. Moreover, LMWHs and fondaparinux have significantly reduced the occurrence of nonanticoagulant side effects of UFH like thrombocytopenia and osteoporosis. Anyhow, a prudent use of these drugs is recommended, as there is always a potential risk because these drugs share the pentasaccharide structure with UFH [43].

For primary prophylaxis of VTE in high-risk orthopedic surgery, LMWHs are clearly more efficacious than UFH, but the incidence of venous thromboembolism remains however unacceptably high [44]. Subcutaneous fondaparinux in its recommended dose of 2.5 mg 6 h after surgery reduces venous thromboembolism by approximately 50 % compared with the LMWH enoxaparin. However, prolonged continuation of prophylaxis with LMWHs or fondaparinux for 30–40 days after discharge from hospital might be complicated if no nursing facilities are available for subcutaneous administration.

Most guidelines recommend 5–10 days of subcutaneous LMWHs for the treatment of acute venous thromboembolism [45]. The initial treatment with UFH, LMWHs, or fondaparinux is followed by bridging with vitamin K antagonists like warfarin. Warfarin is administrated for 3 months if venous thrombosis is provoked by transient risk factors (such as surgery, pregnancy, immobilization, etc.), for at least 6 months if thrombosis is spontaneous, and lifelong in the case of recurrent thrombosis [45, 46].

Actually, chronic atrial fibrillation represents the cardiological condition in which the use of anticoagulant therapy is definitely not satisfactory. In the population of over 60 years, 1 % develops this arrhythmia, with an increase to 10 % at the age of 80. Oral anticoagulant therapy with VKA is highly effective to reduce the rate of ischemic stroke by ≥60 %. In contrast, aspirin is three times less effective than vitamin K antagonists and offers no clear advantage concerning risk reduction of bleeding complications [47]. Unfortunately, adherence to guidelines is still very poor in most health care settings, although efficacy and cost effectiveness of anticoagulant prophylaxis have clearly been demonstrated [48]. It is obvious that there is a clear association between underuse of vitamin K antagonists and poorer outcome. The concern of physicians related to the high risk of bleeding in elderly patients and the poor patient compliance regarding regular drug intake and laboratory monitoring might be an explanation for this phenomenon [49].

Anticoagulants are also used for the treatment of cardiological atherothrombotic conditions like acute coronary syndromes, treated with or without vascular reperfusion techniques including pharmacological thrombolysis or percutaneous intervention. However, there is a need for improvement mainly due to the occurrence of bleeding complications in patients concomitantly treated with multiple drugs that impair hemostasis (UFH, LMWHs, or fondaparinux, administered on top of double or even triple antiplatelet agents like aspirin, ADP-receptor, and platelet glycoprotein IIb/IIIa inhibitors) [50]. To prevent reinfarction, traditional anticoagulants are the cornerstone of therapy. VKAs show high efficacy in this setting and are superior to monotherapy with aspirin [50]. However, they are rarely used by cardiologists due to the need for monitoring and the perceived high risk of bleeding. An oral drug with no need for monitoring would certainly positively influence cardiologists to prescribe anticoagulants for the prevention of secondary myocardial infarction, instead of the platelet function inhibitors currently prescribed [51].

All the above-mentioned limitations could be circumvented to some degree if new drugs with lower risk of bleeding and without the need of laboratory monitoring were available.

Conflicts of Interest None.

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