Chapter 1

An Overview of the Anticoagulant Drugs Used in Routine Clinical Practice

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Abstract

Anticoagulant drugs directly or indirectly influence coagulation factors preventing fibrin formation thus preventing blot clotting. They are classified into two groups according to the mode of application, namely parenteral and oral drugs. Among the latter, vitamin K antagonists (most often warfarin) were the only available oral drugs and were widely used for almost a century. In the recent years, new oral anticoagulant drugs became available that directly target either factor IIa or Xa. This chapter provides an overview of both parenteral and oral anticoagulant drugs used in clinical practice with description of the mode of action and management of therapy in different clinical settings.

Keywords: anticoagulant drugs, indications, therapy

1. Introduction

Anticoagulant drugs directly or indirectly influence coagulation factors and thus inhibit the initiation and progress of coagulation and fibrin-clot formation. They are classified into two groups according to the mode of application, namely parenteral and oral drugs. Among the latter, vitamin K antagonists (most often warfarin) were the only available oral anticoagulants and were widely used for almost a century. In recent years, new oral anticoagulant drugs became available that directly target either factor IIa or Xa [1].

This chapter provides an overview of both parenteral and oral anticoagulant drugs used in clinical practice with a description of the mode of action and management of therapy in different clinical settings.

2. Parenteral anticoagulant drugs

2.1. Unfractionated heparin

Unfractionated heparin (UFH) binds antithrombin—a physiological inhibitor of coagulation—and accelerates its inhibitory action against coagulation factors II and X and in minor degrees also factors IX, XI and XII [2, 3]. UFH is active in a parenteral form only and therefore administered by intravenous (i.v.) infusion [2]. It is used for the treatment of acute thromboembolic events. One of the major disadvantages of UFH is its binding to plasma proteins and endothelial cells making its anticoagulant effect unpredictable [2, 3]. Treatment with UFH must, therefore, be regularly monitored with activated partial thromboplastin time (APTT). Due to different sensitivities of APTT reagents the therapeutic APTT range must be determined by each laboratory and must correspond to heparin anti-factor Xa activity between 0.3 and 0.7 IU/mL [4–6]. Treatment is initiated with UFH bolus of 80 U/kg i.v. and continued with continuous infusion of 18 U/kg body mass/h [7]. Dosage must be adjusted according to the APTT result. At the beginning of treatment, laboratory monitoring is needed several times a day, the first one 6 h after UFH initiation. The two most important non-hemorrhagic side effects of UFH treatment are osteoporosis and thrombocytopenia [2].

2.2. Low-molecular weight heparin

Low-molecular weight heparin (LMWH) is obtained by various methods of fractionation or depolymerization of polymeric UFH [8]. Because LMWHs differ in molecular mass, they also differ in pharmacological characteristics and anticoagulant effects [9]. All LMWHs inhibit coagulation factors II and X. Among the most commonly used LMWHs for treatment and the prevention of acute thromboembolic events are dalteparin (Fragmin®), enoxaparin (Clexane®) and nadroparin (Fraxiparine® and Fraxiparine forte®) in the form of subcutaneous injections. They can also be used as a bridging therapy in patients with high thromboembolic risk during a period when these patients cannot receive oral anticoagulants. Therapeutic dose is determined according to the patient's body weight [2] (**Table 1**).

For prevention of venous thromboembolism (VTE), lower (prophylactic) doses of LMWH are used [2] (**Table 2**). The adequate LMWH dose is selected according to the risk. Prophylactic doses are used in some patients during the interim cessation of oral anticoagulant therapy above all in the first days after large interventions.

The most important advantage of LMWH over UFH is the lower degree of binding to plasma proteins and endothelial cells making their pharmacokinetics and anticoagulant effects predictable [10, 11]. Regular laboratory monitoring with coagulation tests is therefore not needed, except in patients with kidney disease and patients with very low (under 45 kg) or very high (above 120 kg) body weight [2]. Although APTT may be mildly prolonged during LMWH therapy it cannot be used for monitoring. The chromogenic anti-Xa is the test of choice for the determination of plasma LMWH concentration [12]. The LMWH dose should be adjusted to

	Therapeutic dose	
LMWH	Twice daily	Once daily
Dalteparin (Fragmin®)	100 IU/kg BW/12 h sc	200 IU/kg BW/24 h sc
46–56 kg	5.000 IU/12 h sc	10.000 IU/24 h sc
57–68 kg	6.000 IU/12 h sc	12.500 IU/24 h sc
69–82 kg	7.500 IU/12 h sc	15.000 IU/24 h sc
82–120 kg	100 IU/kgBW/12 h sc	18.000 IU/24 h sc
Enoksaparin (Clexane®)	1 mg/kg BW/12 h sc	1.5 mg/kg BW/24 h sc
45–54 kg	50 mg/12 h sc	80 mg/24 h sc
55–64 kg	60 mg/12 h sc	90 mg/24 h sc
65–74 kg	70 mg/12 h sc	100 mg/24 h sc
75–84 kg	80 mg/12 h sc	120 mg/24 h sc
85–94 kg	90 mg/12 h sc	135 mg/24 h sc
94–120 kg	100 mg/12 h sc	150 mg/24 h sc
Nadroparin	(Fraxiparine®) 0.1 ml/10 kg BW /12 h sc	(Fraxiparine FORTE®) 0.1 ml/10 kg BW/24 h sc
50–59 kg	0.5 ml/12 h sc	0.5 ml/24 h sc
60–69 kg	0.6 ml/12 h sc	0.6 ml/24 h sc
70–79 kg	0.7 ml/12 h sc	0.7 ml/24 h sc
80–89 kg	0.8 ml/12 h sc	0.8 ml/24 h sc
90–120 kg	0.9 ml/12 h sc	0.9 ml/24 h sc

IU: International Units, BW: body weight, sc: subcutaneously.

Table 1. LMWH therapeutic doses according to body weight.

LMWH	**Low prophylactic dose (moderate VTE risk)**	**High prophylactic dose (high VTE risk)**
Dalteparin	2500 IU/24 h sc	5000 IU/24 h sc
Enoxaparin	20 mg/24 h sc	40 mg/24 h sc
Nadroparin	0.3 ml/24 h sc	0.4 ml/24 h sc at BW ≤ 70 kg 0.6 ml/24 h sc at BW > 70 kg

IU: International Units, BW: body weight, sc: subcutaneously, VTE: venous thromboembolism.

Table 2. Prophylactic doses of LMWH.

0.5–1.0 IU/mL 4 h after the last LMWH dose when administered twice daily or to 1.0–2.0 IU/mL 5–6 h after the last dose when administered once daily [13, 14]. The two main non-hemorrhagic side effects of LMWH therapy are osteopenia and thrombocytopenia; however, both these side effects are considerably rarer compared to UFH therapy [2].

2.3. Fondaparin

Fondaparin (Arixtra®) is a synthetic pentasaccharide that closely resembles the pentasaccharide naturally occurring in the UFH and LMWH. It is an antithrombin-mediated factor Xa inhibitor that is devoid of any anti-factor IIa (thrombin) activity [15]. It is used for treating patients with acute coronary syndrome and heparin-induced thrombocytopenia. It is indicated also for certain patients with thrombophlebitis in a fixed dose of 2.5 mg daily s.c. Laboratory monitoring is not needed; however, if necessary fondaparin levels should only be determined using assays that use known fondaparin concentrations to generate their calibration curve. The use of fondaparin in patients with creatinine clearance below 30 mL/min is contraindicated [2].

2.4. Hirudin

Hirudin is a naturally occurring peptide in the salivary glands of medicinal leeches that irreversibly inhibits thrombin. Lepirudin, a recombinant hirudin derived from yeast cells, was used in clinical practice but is no longer available. Instead, the synthetic analog—bivalirudin (Angiox®)—with a short half-life is used at percutaneous coronary interventions and for treating patients with heparin-induced thrombocytopenia. The use of bivalirudin in patients with creatinine clearance below 30 mL/min is contraindicated [16].

2.5. Argatroban

Argatroban (Argatra®) is a synthetic reversible direct thrombin inhibitor. It is metabolized solely in the liver and is, therefore, suitable for patients with renal failure. It is used in patients with heparin-induced thrombocytopenia. Treatment with argatroban requires laboratory monitoring with activated partial thromboplastin time (APTT) and the dose adjusted to reach 1.5–3.0 times prolonged baseline APTT, but should not exceed 100 s [17].

3. Oral anticoagulants

3.1. Vitamin K antagonists

The vitamin K-dependent coagulation factors II, VII, IX and X require γ-carboxylation for their procoagulant activity. Treatment with vitamin K antagonists results in the hepatic production of partially carboxylated and decarboxylated proteins with reduced coagulant activity. Among the most commonly used vitamin K antagonists are warfarin and acenocoumarol. Although vitamin K antagonists are absorbed quickly their full effect develops after about 5 days when the activity of all vitamin K-dependent coagulation factors is reduced [1].

Warfarin therapy requires regular laboratory monitoring with prothrombin time (PT). Due to different sensitivities of thromboplastin reagents used for PT measurement the results are expressed as the International Normalized Ratio (INR). For the majority of indications the target INR range falls between 2.0 and 3.0. In certain patient populations, for example, in patients with mechanical heart valves, the target range is 2.5–3.5 INR. A rare non-hemorrhagic

side effect of vitamin K antagonist therapy is skin necrosis that develops at therapy initiation and is a consequence of acute thrombosis of subcutaneous venules and capillaries [1].

3.2. Direct oral anticoagulants

3.2.1. Dabigatran

Dabigatran etexilate (Pradaxa®) is a low-molecular weight prodrug that exhibits no pharmacological activity. After oral administration, dabigatran etexilate is converted to its active form, dabigatran, a potent, competitive and reversible direct thrombin inhibitor [18]. The binding of dabigatran to thrombin is specific and selective and includes both free and thrombus-bound thrombin. Maximal blood concentration of dabigatran is reached after 1–3 h after the intake [18]. About 35% of the drug is bound to plasma proteins. Eighty percent of dabigatran is excreted through the kidneys [18]. Dabigatran half-life is 14–17 h [18]. It is given in fixed doses of either 150 or 110 mg twice daily in patients with atrial fibrillation and 150 mg twice daily in patients with VTE [19, 20]. Prophylactic doses after total hip or knee replacement are 220 or 150 mg once daily with only half the dose given as the first dose after surgery [21].

The anticoagulant effect of dabigatran is predictive and, therefore, requires no regular laboratory monitoring. During dabigatran therapy, APTT and thrombin time (TT) are prolonged, but these two tests can only offer a rough approximation of dabigatran blood concentration. In certain situations when dabigatran concentration needs to be assessed, a specific test must be used, such as modified thrombin time or a chromogenic assay [22, 23].

3.2.2. Rivaroxaban

Rivaroxaban (Xarelto®) directly inhibits factor Xa. It selectively binds both free and prothrombin complex bound factor Xa and in this way inhibits thrombin and clot formation. Peak blood concentration is achieved after 1–3 h after drug ingestion. As much as 95% of the drug is bound to plasma protein. One-third of the drug is excreted through kidneys, the other two-thirds are metabolized in the liver. The drug half-life is 8–13 h [1, 24]. Therapeutic doses are 20 and 15 mg once daily for patients with atrial fibrillation [25]. Patients with VTE are treated with 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily [26, 27]. The drug must always be ingested with food. The prophylactic dose for patients with total hip or knee replacement is 10 mg once daily [28, 29].

No laboratory monitoring of therapy is needed due to the predictive effect of the drug. Rivaroxaban prolongs PT; however, when an assessment of the drug blood level is needed, an anti-Xa test calibrated to rivaroxaban should be used [30].

3.2.3. Apixaban

Apixaban (Eliquis®) directly and reversibly inhibits factor Xa. Maximal blood concentration of the drug is achieved 3–4 h after ingestion. As much as 87% of the drug is bound to blood protein. Twenty-seven percent of the drug is excreted through kidneys and the remainder through the liver. The drug half-life is 12 h [31]. Patients with atrial fibrillation are treated with

5 or 2.5 mg twice daily [32]. Patients with VTE are treated with 10 mg twice daily for the first 7 days followed by 5 mg daily [33]. The prophylactic dose for patients with total hip or knee replacement is 2.5 mg twice daily [34].

No laboratory monitoring of therapy is needed due to the predictive effect of the drug. Apixaban unreliably prolongs APTT and PT. When an assessment of the drug blood level is needed, an anti-Xa test calibrated to apixaban should be used [35].

3.2.4. Edoxaban

Edoxaban directly inhibits factor Xa. Maximal blood concentration of the drug is achieved 1–2 h after the ingestion. About 40–59% of the drug is bound to plasma protein. Roughly 35% of the drug is excreted through the kidneys and the remainder through the liver. The drug half-life is 9–14 h. Therapeutic doses are 60 and 30 mg daily for patients with atrial fibrillation and VTE. The prophylactic dose for patients with total hip or knee replacement is 30 mg once daily. Edoxaban prolongs APTT and PT, but for a quantitative assessment of the drug level, an anti-Xa test calibrated to edoxaban must be utilized [36, 37].

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