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Therapy of venous thromboembolism: anticoagulant treatment

Summary

Treatment of acute venous thromboembolism mainly consists of administration of heparin (usually low-molecular-weight heparin) overlapped and followed by an oral vitamin K antagonist that will be administered for a certain period of time, depending upon the evaluated risk of recurrence and bleeding of each individual patient. Contemporary features include the possibility of reducing the intensity of oral anticoagulant treatment (INR 1.5–2) after an initial full-intensity treatment (INR 2–3) period of 3 to 12 months, and the emergence of new anticoagulant drugs such as fondaparinux and ximelagatran.

Key words: deep vein thrombosis; pulmonary embolism; anticoagulation

Résumé

Dans la grande majorité des cas, le traitement d'un événement thromboembolique aigu consiste en une anticoagulation simultanée par une héparine (en général de bas poids moléculaire) et un anti-vitamine K, la première étant arrêtée dès que le second est effectif. La durée du traitement anticoagulant oral dépendra du risque estimé individuellement de récidive et d'hémorragie. Les éléments nouveaux de ces dernières années concernent la possibilité de réduire l'intensité de l'anticoagulation orale (INR 1,5–2) après une période initiale de 3 à 12 mois de traitement avec une intensité classique (INR 2–3), ainsi que l'émergence de nouveaux anticoagulants dont les premiers représentants sont le fondaparinux et le ximelagatran.

Mot-clefs: thrombose veineuse profond; embolie pulmonaire; anticoagulation

Introduction

This review aims at summarising the present state of the treatment of venous thromboembolism (VTE), a condition that can present with two clinical pictures, deep vein thrombosis (DVT) or pulmonary embolism (PE). In the vast majority of DVT and PE, the treatment consists of the administration of some anticoagulant drug(s) for some period of time. Few patients may, however, benefit from other therapeutic modalities, including thrombolysis and surgical or endovascular embolectomy or thrombectomy. The only established indication for these alternative, mostly experimental treatments, is acute massive pulmonary embolism.

Anticoagulant drugs

From unfractionated (UFH) to low-molecular-weight (LMWH) heparin

The efficacy of UFH for treating established pulmonary embolism (PE) and deep vein thrombosis (DVT) has been demonstrated in two studies, published in 1960 [1] and 1992 [2], respectively. Heparins act via their binding to the natural anticoagulant antithrombin, thereby dramatically accelerating the inactivation of thrombin and several other activated coagulation factors (including activated Factor X, FXa) by antithrombin. Even though UFH can be administered subcutaneously [3], it has mostly been applied as continuous intravenous infusion. Because of a highly individual binding to plasma proteins, including

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platelet factor 4 (PF4), the dosage has to be adapted to the result of blood tests such as the activated partial thromboplastin time (APTT) or, more recently, the anti-FXa activity. The relation between these tests and efficacy (thrombosis recurrence) or safety (bleeding) has, however, never been convincingly demonstrated, at least for the individual patient. Nevertheless, they allow to avoid gross over or underdosage.

During the eighties, UFH was progressively replaced by its low-molecular-weight fractions that have the main advantages of being administered subcutaneously in weight-adjusted doses without requiring monitoring tests in most cases [4]. The mechanism of action of LMWH is similar to that of UFH with a more pronounced effect toward FXa, as compared to thrombin. The clinical equivalence of LMWH and UFH for treating DVT was shown in several studies and anchored in a meta-analysis [5]. One study confirmed this conclusion in the setting of PE [6]. The practical characteristics of LMWH opened the way to outpatient treatment of DVT [7] and, to a lesser extent, PE [8]. Because of their renal elimination, LMWH should be administered with caution in patient with impaired kidney function, especially when the calculated creatinine clearance is below 30 ml/min. In such patients, alternative options include FXa activity monitoring or use of UFH [4] that is cleared via the liver. Practically, creatinine clearance (CrCl) can be approximated by means of the Cockcroft formula CrCl = [(140–age) multiplied by body weight, divided by (0.814 times plasma creatinine level)], whereby weight and creatininaemia are expressed in kg and μmol/L, respectively). For women, the result must be corrected by multiplying the value obtained by 0.85.

In most cases, heparins are overlapped with vitamin K antagonists (VKA) that can be started from the first day of treatment, heparin being stopped as soon as the anticoagulant level induced by VKA has reached an International Normalised Ratio (INR) of 2.0 on two consecutive days. Heparin treatment should, however, last for at least 5 days. It has recently been suggested that cancer patients might benefit more from a prolonged treatment with LMWH

Vitamin K antagonists

Vitamin K antagonists (VKA) block a late step in the synthesis of four plasma coagulation factors (prothrombin or factor II, FII, FVII, FIX, and FX) by the liver. Because of the relatively long half-life of circulating factors, the appropriately stable level of anticoagulation cannot be reached before 4 to 7 days. The VKA include substances with a short (acenocoumarol [Sintrom®]), intermediate (warfarin [Coumadin®]) or long (phenprocoumone [Marcoumar®]) half-life. This feature, associated with a genetically induced metabolic variability [9], the influence of environmental variables such as vitamin K content of food, and the narrow therapeutic window renders close monitoring of VKA treatment necessary and difficult. Monitoring has been standardised, and the therapeutic level corresponds to an INR between 2 and 3 (target 2.5). Below INR 2.0, the risk of thromboembolic recurrence increases, and above INR 3.0, the bleeding risk becomes definitely higher.

The upcoming anticoagulant drugs

Several new anticoagulants are presently under clinical development (fig. 1). They act at the different steps of the plasma coagulation phenomenon. In the present review, we will restrict the discussion to two substances that were recently launched on the market: fondaparinux (Arixtra®) and ximelagatran (Exanta®). Both drugs are registered for thromboprophylaxis in major orthopedic surgery.

Fondaparinux is a synthetic pentasaccharide that is very similar to the smallest component of heparin that can still bind with antithrombin to specifically inhibit FXa. It is administered subcutaneously at a daily dose of 2.5 mg (for up to 30 days following surgery). Compared to LMWH in that setting, fondaparinux reduces the rate of postoperative VTE by about 50% at the costs of a slightly increased risk of major bleeding [10]. In the MATISSE studies, it was shown to be non-inferior at the dose of 7.5 mg/day to SQ LMWH plus warfarin for treatment of established DVT [11] or non-inferior to UFH (continuous infusion) for treatment of established PE [12].

Figure 1

Mechanism of action of new anticoagulant compounds.

A Inhibitors of the tissue factor/factor VIIa pathway.

B Specific inhibitors of factor Xa (example: fondaparinux).

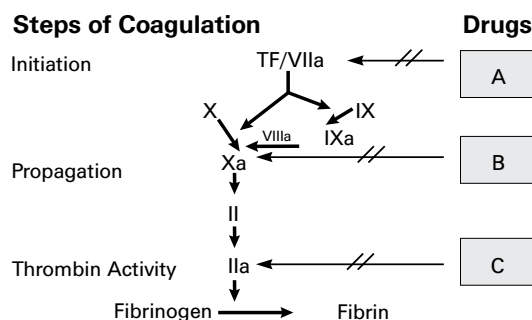C Direct, synthetic thrombin inhibitors (example: ximelagatran).

Steps of Coagulation   **Drugs**

Initiation   TF/VIIa ← A

X → IX
VIIIa   IXa
Propagation   Xa ← B

II

Thrombin Activity   IIa ← C

Fibrinogen → Fibrin

Table 1

Drawbacks of heparins and comparison with fondaparinux and ximelagatran.

Drawbacks of heparins	drawback also present with	
	fondaparinux	ximelagatran
Need for antithrombin	yes	no
Inability to inhibit fibrin-bound thrombin or platelet-bound FXa	no	no
Need for laboratory monitoring (except LMWH)	no	no
Heparin-induced thrombocytopenia	no	no
Lack of oral administration	yes	no
Animal origin	no	no
Narrow benefit/risk ratio	?	?

Ximelagatran is a synthetic, non-peptidic, direct thrombin inhibitor that can be administered orally. The prodrug is transformed in melagatran by the liver. Because of a relatively poor bioavailability, two daily administrations are necessary. It is also registered, in Europe but not in the USA, for thromboprophylaxis in major orthopedic surgery, but only up to 11 days following surgery, at a dose of 24 mg bid. In the THRIVE studies, it was shown to be non inferior at the dose of 36 mg bid to LMWH plus warfarin in established DVT with or without PE [13]. At a reduced dose of 24 mg bid, it was also shown to be superior to placebo for secondary long-term prevention after an initial 6-month classical treatment of DVT [14].

These new drugs do not exhibit most of the drawbacks of heparin (table 1) but liver test abnormalities have been ascribed to prolonged uses of ximelagatran, which led the FDA to reject drug approval. Several other orally active, synthetic FXa and thrombin inhibitors are presently at different stages of their clinical evaluation and some of them look extremely promising.

Adverse effects of anticoagulant drugs

A common adverse effect of all anticoagulant drugs is bleeding that occurs more frequently at the initiation of treatment ("demasking" of lesions) and can have devastating consequences (intracerebral or retroperitoneal bleeds). During that initial period, heparin is associated with a major bleeding risk of 0.8% per day [15]. Major bleeding associated with VKA occurs at a age-dependent [16] monthly rate of about 0.4% [17]. Clinical scores have been prospectively validated and may guide estimation of the haemorrhagic risk under VKA treatment (table 2).

Heparins can produce two types of thrombocytopenia (table 3), one of which being dangerous, the so-called true heparin-induced thrombocytopenia (HIT), that can provoke heparin-dependent platelet aggregation and thrombosis in both arteries and veins. This phenomenon can occur in a few percent of patients given UFH, and is ten times less frequent with LMWH [18].

Coumarin-induced skin necrosis is a very rare complication of VKA that occurs preferentially in protein C and/or S deficient individuals, if large loading doses of VKA are administered, which produces an initial decrease of the short-lived vitamin K-dependent protein C.

A benign, transitory increase of liver enzymes is regularly observed at the initiation of UFH/LMWH therapy but this increase is definitely more pronounced following ximelagatran administration: up to 10% of patients who receive the drug for more than one month experience an ALT increase of more than 3 times the upper limit of normal (ULN) [19]. Even though the clinical relevance of these elevations of liver enzymes remains uncertain, they were found by the FDA to be worrying enough not to allow the new drug be launched in the US market.

Table 2

The Outpatient Bleeding Risk Index (adapted from [36]).

Risk factors		absent	present
Age ≥65 years		0 point	1 point
History of stroke		0 point	1 point
History of GIB		0 point	1 point
Recent MI, Hct <30%, creatinine >133 µmol/L, Diabetes mellitus		0 point	1 point

Classification of patients	low risk (0 point)	intermediate risk (1–2 points)	high risk (3–4 points)
Estimated risk for major bleeding			
in 3 months	2%	5%	23%
in 12 months	3%	12%	48%

GIB = gastro-intestinal bleeding; MI = myocardial infarction; HCT = haematocrit.

	non-immune HIT	**true (immune) HIT**
Occurrence of thrombocytopenia	before day 5	between day 5 and day 21
Platelet count	rarely <100 G/L	<100 G/L or diminution by >50% of initial value
Clinical features	asymptomatic	arterial and venous thromboembolic events
Evolution	transitory and regression; normalisation within 3 days	persistent (if treatment is continued); normalisation within 3–7 days following heparin discontinuation
Incidence	about 10%	0.5 to 5%

Intensity of oral anticoagulant treatment

The usually recommended intensity of oral anticoagulation corresponds to an INR range of 2 to 3. As a matter of fact, low-intensity anticoagulant treatment with an INR 1.5–2.0 has recently been demonstrated to be strikingly more effective than placebo in patients who were initially treated during at least 3 months with a classical INR of 2 to 3 after a venous thromboembolic event [20]. The possibility of reducing the intensity of anticoagulant treatment after an initial period of "full" anticoagulation has become a realistic option at least in some patients [21] in order to reduce the bleeding risk while maintaining some protection against thromboembolic recurrence, which was, however, questioned by a Canadian trial that found a similar bleeding risk and a lesser antithrombotic effect in patients treated at a low-intensity INR, compared with patients treated at full-intensity [22]. The extremely low bleeding risk observed in this trial is at variance with all previous trials on anticoagulant treatment, which suggests that the study population was not representative of real life.

Duration of oral anticoagulation following DVT

The duration of anticoagulant treatment following deep vein thrombosis (DVT) and pulmonary embolism (PE) remains controversial. Nevertheless, several facts have been highlighted in the past two decades that should help to suggest guidelines driven by evidence rather than by changing opinions of leaders in the field. Obviously, the duration should be dictated by the balance between two risks: that of recurrent venous thromboembolism (VTE) and that of treatment-induced haemorrhage. Evidences regarding this balance include:

– according to a meta-analysis of 25 studies [23], recurrent DVT or PE is rather rare during anticoagulant treatment (8.8%; 95% confidence interval [CI]: 5.0–14.1%) with a fatality rate of only 0.4% (95% CI: 0.2–0.6%);

– recurrences occur preferentially during the initial three weeks after the start of treatment, and concern mainly patients with cancer (odds ratio [OR] 2.7), chronic cardiovascular disease (OR 2.3), chronic respiratory disease (OR 1.9) and other clinically significant medical disease (OR 1.8) [24];

– anticoagulant treatment is associated with a definite bleeding risk: heparin induces major bleeding at a rate of 0.8% per day (with a daily fatality rate of 0.05%) [15], and oral anticoagulants in 0.4% per month [17].

These data allowed the construction of clinical decision-analysis Markov models suggesting that a 3-month duration of oral anticoagulant treatment is appropriate in the average patient [25] and that treatment duration should not exceed one year even in patients with the Factor V Leiden, a common thrombophilic mutation [26]. Hard data, however, originated from well conducted randomized clinical trials (some of which were combined in a recent meta-analysis [27]). These data include the following evidence:

– risk of recurrent VTE is 40% lower in patients treated for 12–24 weeks compared with those treated for 3–6 weeks without significant difference in major bleeding risk [27];

– VTE related to temporary risk factors is associated with a definitely lower risk of recurrence [27–29];

– after a follow-up of two years, the recurrence rate was 18.1% in patients treated for 6 weeks compared to 9.5% in those treated for 6 months [29];

– in a small group of selected high-risk patients with idiopathic DVT [30], the an-

Table 4.
Proposed duration of anticoagulant treatment following VTE[1].

3 to 6 months
First event with reversible or time-limited risk factor[2] (patient may have underlying Factor V Leiden or prothrombin 20210)
6 months
Idiopathic VTE, first event
12 months to lifetime
First event[3] with cancer (until resolved), anticardiolipin antibody, or antithrombin deficiency
Recurrent event, idiopathic or with thrombophilia

[1] All recommendations are subject to modification by individual characteristics including patient preference, age, comorbidity, and likelihood of recurrence;

[2] Reversible or time-limited risk factors: surgery, trauma, immobilisation, estrogen use;

[3] Proper duration of therapy is unclear in first event with homozygous factor V Leiden, homocystinaemia, deficiency of protein C or S, or multiple thrombophilias; and in recurrent events with reversible risk factors.

nual recurrence rate was 27.4% in patients given oral anticoagulants for three months compared with 1.3% in patients treated for two years; in the latter group, major haemorrhage occurred in 3.8% compared with 0 in the shorter treatment duration group;

– after two years of follow-up, DVT patients who were treated for one year had a recurrence rate of 15.7% compared to 15.8% in patients treated for three months [31], suggesting that the clinical benefit associated with extending the duration of anticoagulant therapy to one year is not maintained after the therapy is discontinued;

– after a second episode of VTE, one study showed that the cumulative recurrence rate was 20.7% after 4 years in patients treated for 6 months compared with 2.6% in those treated indefinitely; the corresponding rates of major bleeding were 2.7% and 8.6% [32].

Based on all these considerations, the ACCP experts consensus [33] recommended durations of anticoagulant treatment that are summarised in table 4. Amazingly, these experts also suggested to consider life-time anticoagulation in case of idiopathic thromboembolic events, a suggestion that is unlikely to have a favorable benefit/risk ratio except in patients at very low risk of bleeding.

Another interesting approach to better tailor individually duration of anticoagulant treatment would be to recognise which patients are at lower or higher risk to present a recurrent event. For example, the ongoing REVERSE study aims at developing a clinical prediction rule to identify low recurrence risk

in patients with idiopathic venous thromboembolism. Other authors tried to use D-dimer levels to predict the risk of recurrent event. Thus, Palareti et al. [34] showed that following idiopathic DVT, a normal D-dimer value (<500 ng/ml) one month after cessation of oral anticoagulant treatment, had a high negative predictive value for VTE recurrence. In a similar attempt to better evaluate the risk of recurrence after a first DVT, Prandoni et al. [35] showed that the presence of residual venous thrombosis is an important risk factor for recurrent thromboembolism. However, the exact instructions for use of these interesting new features remain to be established.

Conclusions and perspectives

Anticoagulation is the therapeutic option in most patients with established DVT or PE. Treatment is usually initiated with LMWH overlapped and followed by VKA. Treatment duration after VTE must be individualised, with shorter duration in case of distal DVT, temporary risk factor, or increased bleeding risk, and longer duration in case of a recurrent event, especially if permanent risk factors are present. After an initial 3 to 12-month course of full-intensity (INR 2–3) VKA, dose can be reduced to target INR 1.5 to 2, at least in selected patients in whom prolongation of treatment appears desirable. In the near future, fondaparinux might replace LMWH in the initial treatment of VTE and ximelagatran – or, more probably, other novel, orally active anticoagulant drugs – replace both heparins and VKA.

Because VTE is a chronic, recurrent disease, long-term anticoagulant therapy would be ideal in a substantial proportion of patients after a first episode of VTE. This goal is hampered by the bleeding risk induced by all presently available anticoagulant drugs. Nevertheless, empirical recommendations on duration of anticoagulant treatment following acute VTE have been more and more replaced by evidence-based guidelines but there are still several situations for which treatment durations are uncertain.

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