Anticoagulation in clinical practice. Part II: the use of heparins

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Abstract

The authors review, in this, the second part of the theme "anticoagulation in clinical practice", the use of heparins in clinical practice. Firstly, the use of unfractionated heparin, is discussed along with the indicated uses in inpatients, with often consequent long admission times, as well as the disadvantages of its use for outpatients e.g. difficult use at home and complex monitorisation. Secondly, the authors present low molecular weight heparins, which combine easy administration with easy monitorisation, making their total cost lower than that of unfractionated heparin. Caution must be exercised in their implementation, as each low molecular weight heparin has an individual profile that must be assessed in each clinical situation. To date, all studies point to a beneficial effect with the use of the various unfractionated heparins in their different clinical settings. It seems probable that new indications will appear.

Key words: unfractionated heparin, low-molecular weight heparin, thrombocytopenia, anti-Xa activity.

Unfractionated heparin

Mechanism of action

Heparin is a naturally-occurring polysaccharide polymer, derived from bovine or porcine in its commercialized forms. Its main mechanism of action is the inhibition of factor (F) Xa and F IIa (thrombin) when mediated by antithrombin III (AT III), and inhibition of F IIa when mediated by heparin cofactor II (HC II). Its molecular weight (MW) ranges from 9.000-15.000 Daltons (D). Heparin is comprised of 3 domains. Domain 1 is formed by a pentasaccharide, which strongly binds to AT III to inhibit F Xa. Domain 2 has weak heparin-binding to AT III, and is not capable of speeding up the inhibition of AT III by itself, which allows AT III and FXa to draw nearer. Domain III acts jointly with the other two, speeding up the inhibition of AT III against F IIa, through a strong binding, and it is at this site where heparin binds to F IIa. Heparin can also act through the activation of HCII, with an anti-FIIa activity, albeit with poorer performance than that of AT III, which requires high doses of heparin.[1,2]

Pharmacokinetics

Heparin is poorly absorbed by the gastrointestinal system; therefore, it is administered intravenously (iv) or subcutaneously (sc). After administration, it circulates bound to plasma proteins. There is an initial phase of rapid clearance, followed by a more gradual clearance. The distribution volume is 40-60 mL/kg. The dose-response relation is not linear. The anticoagulant response increases disproportionally in intensity and duration as the dose increases; therefore, it is unpredictable and requires strict monitoring. The increase in half-life is related to an increase in the dose. Thus, following a bolus injection of 100U/kg/weight iv., the biological half-life is 56 minutes, and 152 minutes for a bolus of 400U/kg/weight.

Clearance is renal, in the form of depolymerized, less sulphated molecules, which contain only 50% of their initial activity. The influence of hepatic and renal diseases in the pharmacokinetic of classic heparin is controversial, with various contradictory results being obtained.

Subcutaneously, heparin has a bioavailability of around 10-20%, and due to its half-life, it requires 2-3 administrations daily.[3]

Monitoring

Monitoring of heparin therapy is done by determining aPTT, which should be kept within a certain therapeutic range, usually 1.5-2 times the control. Monitoring should be performed closely in case of intravenous (iv) therapy. When sc. administration is used, the

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therapy is monitored less frequently, or not at all.[4]

For oral anticoagulants, cases of resistance to heparin have been reported. Around 25% of the patients who take heparin required more than 35.000 U/day of unfractionated heparin in order to change the aPTT levels. When this amount exceeds 40.000 U/day, it is a case of resistance, which may occur through the increase of F VIII and other procoagulants. In this case, the aPTT is too short before therapy, with anti-Xa activity within the therapeutic values or else, when both parameters are low, other situations should be considered, such as the increase of heparin binding plasma proteins, increase of heparin clearance (as described in cases of pulmonary embolism) and AT deficit (usually only in congenital conditions, where the AT level is below 25%). If we find this type of patient with poor response to heparin, the anti-Xa activity should be monitored, therapeutic values of which between 0.3 and 0.7 UI/L.[5,6,7]

TABLE I

Categories of risk to venous thrombosis after surgery

HIGH RISK
General surgery in patients > 40 years, with history of thromboembolism
Extensive abdominal or pelvic surgery for malignancy
Major orthopedic surgery of the lower limbs
MODERATE RISK
General surgery in patients > 40 years, with duration > 30 minutes
LOW RISK
Uncomplicated surgery in patients < 40 years without risk factors
Minor surgery in patients > 40 years without additional risk factors

Indications

The main indications of standard therapy with heparin are: 1) prophylaxis of deep vein thrombosis in high-risk clinical/surgical patients, with administration of 5.000 U 12/12 hours sc., and higher doses (10.000 U 12/12 hours sc.) in the cases associated with congestive heart failure and coronary disease - unstable angina and acute myocardial infarction (in the prevention of mural thrombus, death and repeat stroke and after thrombolytic therapy); 2) treatment of venous thromboembolism and acute arterial embolisms, administering around 1.000 u/hour iv in continuous infusion, but adjusted to a aPTT of 1.5-2.5 times the control, until optimal oral anticoagulation is reached; in this case, combined therapy is usually necessary for 5-7 days.[4] In surgical patients, the classification of risk groups is important, considering, as high risk, those with deep vein thrombosis (DVT) - 40% of cases and fatal pulmonary embolism (PE) - 1-5% of cases. The low risk group involves DVT, which occurs in less than 10% of cases and fatal PE, with less than 0.01% of cases; the remainder falls into the moderate risk group (*Table 1*).[8]

In case of relapsed thromboembolism refractory to oral anticoagulants, portable external or implantable pumps can be used for continuous iv infusion. These infusion pumps can also be used in patients with chronic disseminated intravascular coagulation, and in pregnant women with thromboembolism, in whom oral anticoagulants are contraindicated, although in practice, low molecular weight heparin is more commonly used.[4] Heparin is also used for hemodialysis, in the extra corporeal circulation in cardiopulmonary bypass during the use of intraaortic balloon, in cardiac catheterization, in procedures of coronary recanalization, and in acute myocardial infarction and unstable angina. *Table II* lists the usually recommended doses.[5]

Adverse effects

The main complication of therapy with heparin is hemorrhage, therefore close monitoring is essential.[4] For patients receiving heparin, intramuscular therapy should be avoided due to the risk of hemorrhage. This risk is increased in the patients receiving antiplatelet drugs.[4] Another adverse effect is thrombocytopenia,[4,9,10] defined as below 150000 platelets/mm after the 5th day of therapy, or earlier if there is previous exposure to heparin. Thrombocytopenia corresponds to an idiosyncratic reaction associated with the treatment with heparin, particularly heparin from bovine source, and occurs in approximately 10% of the patients treated with this drug. Therefore, it is important to monitor platelet levels during treatment. This situation results in the production of anti-heparin IgG during treatment (even in lower doses), which reacts with the heparin that binds to the platelet factor IV; this complex binds to the platelets through antibody Fc receptors, forming platelet

TABLE II

Dosage for unfractionated heparin

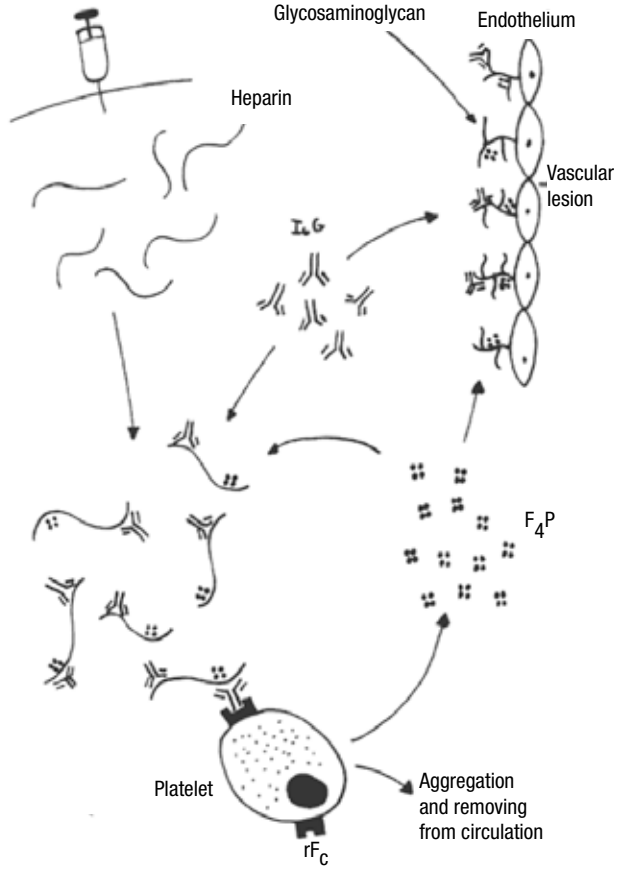
Indication	Dose
Prophylaxis of DVT and PE	5000 U sc every 8 or 12 hr
Treatment of VTE	bolus 5.000 U, followed by 30.000 - 3500 U/24h iv or 35.000 - 40000 U/24h sc adjusted for aPTT 1.5-2.5x control
Unstable angina	bolus 5.000 U, followed by 24.000 - U/24h iv adjusted for aPTT 1.5-2.5x control
Acute myocardial infarction Prevention of mural thrombus, death and repeat stroke	12.500 U sc, twice/day
After thrombolysis with rTPA	bolus 5.000 U, followed by 24.000 U/24h iv adjusted for aPTT 1.5-2.5x control
After thrombolysis with SK	bolus 2.000 u, followed by 12.500 U sc twice/day

DVT - Deep vein thrombosis; PE - Pulmonary embolism; VTE - venous thromboembolism; rTPA - recombinant tissue plasminogen activator; SK - Streptokinase

aggregates and being removed later (*Fig. 1*). This binding promotes even more release of platelet factor 4 to the plasma from the granules. In the vascular wall, on the surface of endothelial cells, there are glycosaminoglycans similar to heparin, which form the same type of complexes with antibody specificity, and which promote the vascular lesion of thrombosis (also favored by the presence of platelet aggregates). In these thromboses, the treatment consists in the suppression of heparin. There is variability in the platelet reactivity to antibodies, therefore only some patients will develop thrombosis.

Another complication of treatment with heparin is osteoporosis, which is associated with prolonged treatments lasting over two months.[4] Classic heparin also promotes the release of lipolytic enzymes such as lipoprotein lipase, and increases the free fatty acids and triglycerides that incite atherosclerosis.[11]

The reversion in case of intoxication is obtained with protamine sulphate, but suspending treatment is sufficient in milder cases.[4] 10 mg of protamine sulphate is necessary to neutralize 1.000 U of heparin. It



F_4P - Platelet Factor 4; rF_c - immunoglobulin receptors

Mechanism of thrombocytopenia and thrombosis associated with heparin.

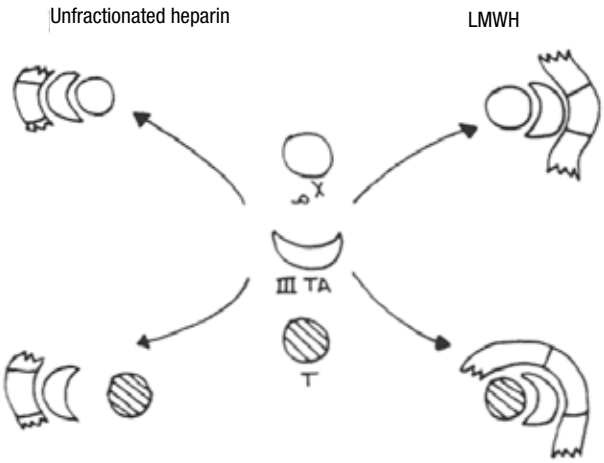
FIG. 1

is important to bear in mind that when a continuous infusion is interrupted, half of the doses administered in the previous hour are invalidated: when an infusion of 1.000 U/H is suspended, there are 500 left to neutralize. Intravenous administration should be slow, to prevent possible secondary effects of this drug i.e. high blood pressure, bradycardia, dyspnea, nausea and vomit.

Low molecular weight heparin

Structure and mechanism of action

Low molecular weight heparins (LMWH) are produced through the depolymerization (chemical or enzymatic) of unfractionated heparin, which is controlled, to prevent degradation of essential pentasaccharides. Their MW ranges from 3.000 to 8.000 D. Changes in



LMWH with factor Xa (Xa) and thrombin (T) through antithrombin III (ATIII).

Difference between the interaction of unfractionated heparin and low molecular weight heparin.

FIG. 2

the sites that bind to AT III and HC II can occur as a result of depolymerization. Lower molecular weight heparins (2.000-2.500 D) have only domain 1, and higher molecular weight heparins (5.000-13.500 D) can have all three domains.[12]

The primary determining factors for their anticoagulant action are AT III-dependant inhibition of FXa and thrombin. On the other hand, only chains with more than twenty monosaccharides, i.e. over 5.400 D, including high-affinity pentasaccharide, can catalyze the inhibition of thrombin. For the inhibition of thrombin, an interaction with the domain 1 of heparin is required, which is not necessary for factor Xa (*Fig. 2*), this being the main reason why the anti-Xa activity of LMWH exceeds its antithrombin activity. Therefore, for the standard heparin, the FXa/F IIa inhibition activity ratio is 1:1, while for LMWH the ratio ranges from 2:1 to 4:1 (the heavier the molecule, the lower the ratio).[13,14,15] Each LMWH differs from the remaining in the characteristics of distribution of the MW, specific activities (measured by the abovementioned ratio), plasma clearance levels and recommended doses. Therefore, an investigation on LMWH cannot be generalized and individual studies should be carried out.[16]

It is known today that its antithrombotic activity is not reduced to the inhibition of F Xa (and to a lesser extent F IIa), as there are other mechanisms under investigation, namely activation of the fibrinolytic system. In this sense, it has been observed that from the third day of administration, increases in tPA from the vascular endothelium, increases in the thrombin--AT complexes, of the fibrin and D-dimer degradation products, changes to the rheological status and modulation of the platelet/vascular endothelium interaction are observed.[1,3,17]

These are produced through several depolymerization processes, which explain its heterogeneity, and are sold in the form of sodium or calcium chloride. Nadroparin, reviparin and dalteparin are obtained through depolymerization with nitrous acid. Enoxaparin and bioparin through alkaline depolymerization (with b-clearance), parnaparin through peroxidative reaction, and finally, tinzaparin through enzymatic depolymerization (using heparinase from Flavobacterium heparinum).[3,12,18] Currently, second and third generation heparins with other characteristics have been developed, known as 'ultra low' molecular weight heparin.[3]

In Portugal, nadroparin calcium (Fraxiparina®), reviparin sodium (Clivarin®), dalteparin sodium (Fragmin®) and enoxaparin (Lovenox®) are currently being commercialized. These heparins are available in vials or syringes dosed for anti-Xa activity according to the quantity of drug.

Pharmacokinetics

Its binding to plasma proteins, endothelial cells and macrophages is less strong than that of classic heparin, thereby allowing for greater anticoagulant activity, due to the higher bioavailability to interact with antithrombin. In the classic heparin, the unpredictable response reflects the wide variability in the plasma concentration of heparin-binding proteins.[19]

Clearance occurs in two stages, and is dose--dependent: a rapid, saturable phase, reflecting the hepatic uptake, and a slow phase, corresponding to renal clearance.[19]

The higher bioavailability, dose-dependent clearance and lower affinity to heparin-binding proteins make the anticoagulant response more predictable, and as a result, monitoring being usually unnecessary.[19]

Advantages

These heparins have a longer half-life (allowing for a

TABLE III

Dosage for low molecular weight heparin

	Prophylaxis	Treatment
Fraxiparine®	7500 ICU anti-Xa – MR 100-150 ICU anti-Xa/kg-HR	225 ICU anti-Xa/kg/12 hours
Fragmin®	2500 IU anti-Xa - MR 5000 IU anti-Xa - HR	100-120 IU anti-Xa/kg/12 hours
Iovenox®	20 mg - MR 40 mg - HR	1 mg/kg/12 hours
Clivarin®	1750 UI anti-Xa/day	Not determined

MR - Moderate risk; HR - High risk

single administration daily), bioavailability of 90% sc and lower risk of haemorrhage.[3] This lower hemorrhagic risk reflects the lower inhibition of the platelet functions (less binding to platelets), the non-increase of micro vascular permeability and lower interference with the interaction between platelets and vascular wall (poorer affinity with endothelial cells, platelets and von Willebrand factor).[19] In most of the cases, laboratory monitoring is not required, which makes it easier to use this drug. Other advantages include lower clearance of lipolytic enzymes, lower association with osteoporosis, safety for pregnancy and lower activation of platelets (and, consequently, lower cases of thrombocytopenia) compared with unfractionated heparin.[9,11,19]

Monitoring

In clinical practice, these patients are monitored through the aPTT in human plasma (by measuring the effect of heparin in the thrombin-thrombin IXa and XIa group), or amidolytic anti-Xa assay in human plasma (which assess the effect on the inhibition of F Xa), with the latter being most frequently used, since aPTT usually does not undergo significant changes.[20,21] In the amidolytic assay, human plasma can be replaced by purified AT III, but plasma is preferable, since the interactions with plasma proteins more closely simulate what occurs in vivo. Nevertheless, because LMWH are polyelectrolytes that interact with blood cells and vessels, sometimes plasma measurements do not reflect the actual plasma level.[3] It is determined 3-4 hours after administration, and only in selected cases, namely in obese or low weight individuals, in patients with renal insufficiency (due to the risk of accumulation of the drug) and in patients with hemorrhagic or thrombotic episodes, when prophylactic doses are used.[19] When therapeutic doses are used, this monitoring is performed at the beginning of the treatment and periodically during the treatment, but recent studies have shown that monitoring is likely to be dispensable, the determination being restricted to cases of prophylaxis. Monitoring in these cases is justifiable because overdose or adverse effects can occur more easily in these groups. The administration is done at fixed doses, but if a more close adjustment of the doses is desired, then the patient's body weight and/or hemorrhage risk must be considered. Adjustment by measuring the biological activity is usually difficult and is not commonly used. These heparins are antagonized by protamine sulphate, to varying degrees, depending on the heparin used.

Indications

These heparins are indicated for use in the prophylaxis of thromboembolism in general surgery, orthopedic surgery, acute, and polytraumatized lesions of the spinal cord, where they are similarly effective, with lower hemorrhagic risk than that of unfractionated heparin.[19] Following femoral-popliteal bypass, it is observed that they are more effective than aspirin and dipyridamole in the maintenance of patent bypass after 1 year.[19] They do not seem to be effective in reducing the incidence of restenosis after coronary angioplasty.[19] For prophylaxis, a single administration daily is used. They are used simultaneously with venous compression measures (wearing of elastic stockings), placing lower limbs in a higher position, respiratory kinesitherapy and early mobilization after surgery. *Table III* lists the recommended doses for each of the indications already used and for each drug.[22]

Monitoring of platelets is essential in all patients, although the incidence of thrombocytopenia is lower than with classic heparin. Monitoring of anti-Xa activity is usually performed only in the abovementioned cases. Ideal levels are between 0.1-0.2 UI/mL, and should not exceed 0.2 UI/mL 3 hr after administration. In the patients with renal insufficiency, the dose should be adjusted (usually to half of the dose).[23,24,25,26]

They are also indicated for the treatment of deep vein thrombosis.[19] Two recent studies indicate that

LMWH that are not monitored are equally safe and effective compared with unfractionated heparin, in patients with pulmonary embolism, in whom unfractionated heparin is considered the treatment of choice for most of the patients, except when there is hemodynamic instability, requiring thrombolytic therapy. Therefore, the use of LMWH may be extended to patients with pulmonary embolism, after ruling out of hemodynamically unstable patients, representing an appropriate alternative to unfractionated heparin. Reviparin sodium and tinzaparin[27,28] were tested. In treatment, the anti-Xa activity should also be monitored, to a therapy level of 0.5-1.0 UI/mL. This determination should be done for all patients at the beginning of their treatment. Another important determination at the beginning of the therapy is that of hemoglobin, platelets, creatinine and aPTT (the latter shows few variations throughout the treatment). aPTT and anti-Xa activity should be evaluated daily until day 5, and then evaluated every 5 days. The determination of platelets should be done at the beginning of the treatment, on day 6 and then twice a week. The repetition of hemoglobin and creatinine tests is only justified if there are baseline chances. Complications include hemorrhage (rare) and allergic reactions. The administration is via sc, with 2 administrations daily followed by oral anticoagulation for at least 3 months.[15,16,29,30]

For secondary prophylaxis of vein thrombosis, after 10 days of administration of unfractionated heparin, LMWH seem to be more effective than warfarin over 3 months, in patients with a high risk of hemorrhage and in those in whom monitoring is difficult, representing a good alternative.[19] In unstable angina, they seem to be at least equally effective and more practical, but should not exceed 100 U anti-Xa, since higher doses seem to cause a higher number of hemorrhages. In patients with ischemic stroke, they are superior to placebo in regards to mortality or dependence of daily activities, with equal risk of hemorrhagic transformation.[19] LMWH seem to be advantageous for thrombolysis or coronary angioplasty, since that at the site where the plaque rupture or arterial lesion occurs, there is high platelet activation and these heparins do not appear to be inhibited by the platelet factor 4.[14] They also appear to be effective in preventing post-angioplasty stenosis, through the inhibition of the proliferation of smooth-muscle cells, which constitutes the main mechanism involved in the late stenosis after successful angioplasty; experience in this area exists primarily with reviparin. The activity of this heparin seems to be mediated by the TFPI (tissue factor pathway inhibitor), which is an important endogenous inhibitor of coagulation and platelet activation, acting in a synergic manner with heparin.[31,32] We found the same results relating to peripheral arterial thrombosis (post-thrombolytic and post-angioplasty therapy).[11,33,34]

These heparins should not be administered in patients with heparin-induced thrombocytopenia, as high cross-reaction occurs with the antibody that causes this condition. Alternatively, danaparoid sodium should be used, which has a lower cross-reaction.[19]

Conclusions

In conclusion, heparins have clear advantages over oral anticoagulants, particularly in some conditions in which its use is mandatory (such as the case of pregnancy). Their effects can be easily controlled, which is frequently the case in surgery. However, they have undesirable effects in a significant percentage of cases, which seem to occur less frequently and with less severity when LMWH is used, requiring less monitoring. These heparins have gradually replaced the unfractionated heparin and, in some cases, they seem to have new effects that are not shared with classic heparin. Nevertheless, we should be careful when administering this drug, and further studies need to be carried out, to determine the right dose for each heparin and the appropriate therapeutic application, which seem promising. ■

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