Drug Update

LOW MOLECULAR WEIGHT HEPARINS

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Heparin was discovered rather accidentally by J McLean, a medical student in 1906. It was named heparin as it was thought to be abundant in the liver. It has been used for over fifty years in the acute management of venous thrombosis and pulmonary embolism. Its role has also emerged in arterial thrombotic events particularly in unstable angina, myocardial infarction and acute peripheral arterial occlusion. It was used earlier only in the unfractionated form. One of the major limitations of conventional heparin is that its use requires constant monitoring of activated thromboplastin time (APTT). Consequently it can only be administered to a hospitalized patient. Adverse effects like bleeding, heparin induced thrombocytopenia and osteoporosis on prolonged use may be troublesome. Over the past decade newer heparins, the low molecular weight heparin (LMWH) have emerged. They are prepared from unfractionated heparin by enzymatic or depolymerisation methods (Table 1). They can be given safely on outpatient basis without any monitoring and appear to have fewer side effects [1]. They are already widely replacing heparin in Europe and North America[2].

TABLE 1

Low molecular weight heparin preparations

Preparation	Method of preparation	Molecular weight
1. Ardeparin	Peroxidative depolymerisation	6000
2. Dalteparin	Nitrous acid depolymerisation	6000
3. Enoxaparin	Alkaline depolymerisation	4200
4. Nadroparin	Nitrous acid depolymerisation	4500
5. Reviparin	Nitrous acid depolymerisation	4000
6. Tinzaparin	Heparinase digestion	4500

Structure and Mechanism of Action

Like heparin, LMWH are glycosaminoglycans, consisting of chains of alternating residues of D-glucosamines and uronic acid, either glucoronic acid or iduronic acid. Heparin is a heterogenous mixture of polysaccharide chains varying in molecular weight from 3000 to 30,000. whereas LMWH have chains with a mean molecular weight of 5000. Both heparin and LMWH exert their anticoagulant activity by activating antithrombin (earlier called antithrombin III), which accelerates the inactivation of coagulation enzymes thrombin (factor IIA), factor Xa and factor IXA. This interaction with antithrombin is mediated by a unique pentasaccharide sequence. Binding of pentasaccharide to antithrombin causes a conformational change in antithrombin that accentuates its action with thrombin and factor Xa by about a thousand times. To inactivate thrombin, drug must bind to both thrombin and anti thrombin, thereby forming a tertiary complex. This complex can only be formed by pentasaccharides-containing heparin chains comprised of at least 18 saccharide units. Most of the chains of heparin have at least 18 saccharide units, whereas fewer than half of LMWH chains are of this length. More simply put, heparin fragments can only bind to both antithrombin and thrombin when they exceed a molecular weight of 5000. Fragments of smaller size (LMWH) can not bind to both antithrombin and thrombin, but can bind to antithrombin and factor Xa and catalyze the inactivation of factor Xa. Consequently heparin has equivalent activity against antithrombin and factor Xa but LMWH has a greater activity against factor Xa.

Pharmacokinetics

LMWH produce a more predictable anticoagulant response than heparin because of their better bioavailability, longer half life and dose-independent clearance[2]. LMWH have a plasma half life two to four times that of heparin and are mainly eliminated by the kidneys. Elimination is slower and independent of dose. This permits less frequent dosing, Heparin is eliminated in two phases: a rapid saturable phase reflecting hepatic uptake, and a slower phase corresponding to renal clearance. Pharmacokinetic differences between heparin and LMWH are explained by the lesser property of LMWH to bind to plasma proteins, endothelial cells and macrophages compared to heparin. Heparin also binds to platelet factor 4 (released from activated platelets), and high molecular weight multimers of von Willebrand factor. Some of

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the heparin binding proteins are acute phase reactants and their concentrations are increased in ill patients, whereas platelet factor 4 and von Willebrand factor are released during the clotting process. This causes an unpredictable anticoagulant response with heparin[3]. All LMWH are recommended to be administered subcutaneously (SC) and monitoring of APTT is not required.

Clinical Uses

Prophylaxis: Anticoagulants are required to prevent the risk of perioperative deep vein thrombosis and fatal pulmonary embolism after major general surgery, orthopaedic surgery like hip and knee transplants, spinal cord injury and multiple trauma. The risk is increased with increased duration of surgery, increasing age and the presence of co-morbid conditions like coronary artery disease, malignancy and thrombophilic states. LMWH are probably more effective than heparin and warfarin[4]. Dalteparin or Enoxaparin in a dose of 2500 units SC 1 to 2 hours before general surgery followed by once daily for 10 days is recommended in high risk cases. In high risk orthopaedic cases 5000 units SC may be started 12 hours after the surgery.

Therapeutic: In deep vein thrombosis LMWH have been shown to more effective and cause fewer major bleeding complications than heparin[5]. Dalteparin or Enoxaparin in a dose of 100 units per Kg body weight SC twice a day are recommended. Same dose is recommended in unstable angina. Although considered, as effective as heparin in unstable angina, a recent study has shown reduced incidence of myocardial infarction with LMWH [6].

Adverse effects

Adverse effects are similar to heparin except that their incidence is reduced. Bleeding, thrombocytopenia and osteoporosis occur less frequently [2,7]. Anaphylactoid reaction can occur. Non-surgical bleeding due to overdosage of LMWH is not as easily reversed by protamine as with heparin. In patients of heparin induced thrombocytopenia, LMWH cannot be used because of cross-reactivity. Although they are more costly than heparin, cost advantage of heparin is offset by the cost of hospitalisation and frequent monitoring. With LMWH monitoring of APTT is not recommended except of renal failure and those who have a body weight less than 50 Kg or more than 80 Kg. Like heparin LMWH are safe in pregnancy.

Conclusion

With LMWH, there is convenience in once daily administration of 'fixed dose' for prophylaxis and weight adjusted, un-monitored dose for treatment. Out-patient therapy is safe, efficacious and cost effective. The incidence of bleeding, heparin-induced thrombocytopenia with complicating thromboembolism and osteoporosis is reduced.

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