The British Society for Haematology Guidelines on the use and monitoring of heparin 1992: second revision. BCSH Haemostasis and Thrombosis Task Force.

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The British Society for Haematology Guidelines on the use and monitoring of heparin 1992: Second revision

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Properties of unfractionated and low molecular weight heparin

CHEMISTRY OF HEPARIN

Unfractionated heparin is a naturally occurring glycosaminoglycan produced by the mast cells of most species. It is extracted from porcine or bovine mucosa, all the products currently used in the United Kingdom being of porcine origin. It consists of alternating chains of uronic acid and glucosamine, sulphated to varying degrees, and has a molecular weight range of 5000–35 000, with a mean of about 12 000–14 000.

Low molecular weight heparin is manufactured from unfractionated heparin by controlled depolymerisation using chemical (nitrous acid or alkaline hydrolysis) or enzymatic (heparinase) methods. Although these processes yield different end groups, there is no evidence that these differences in chemical structure affect biological function. The biological properties of any low molecular weight heparin are primarily determined by its molecular weight distribution. The products currently available have an average molecular weight between 4 000 and 6 000, and 60–80% of the total polysaccharides lie between 2 000 and 8 000.

ANTICOAGULANT ACTIVITIES

All anticoagulant activities of unfractionated heparin and low molecular weight heparin depend on the presence of a specific pentasaccharide sequence which binds with high affinity to antithrombin III (AT III) and potentiates its activity[2]; this sequence is present in about one third of the chains in unfractionated heparin but in lower proportions in low molecular weight heparin because some of these sequences are destroyed by the depolymerisation process. Acceleration of inhibition of factor Xa (anti-Xa activity) requires only the pentasaccharide sequence (approximate molecular weight 1700), but potentiation of thrombin inhibition (anti-IIa activity, also prolongation of APTT) requires a minimum total chain length of 18 saccharides (molecular weight approximately 5400).[3] Therefore, in all low molecular weight heparin preparations the anti-Xa activity is greater than the anti-IIa or APTT activity. In the low molecular weight heparins currently available the ratio of anti-Xa to anti-IIa activity ranges from 1·8 to 3·5.

STANDARDISATION

When initially developed, low molecular weight heparins were assayed against the unfractionated heparin standard by a variety of different methods and the units for the different products could not readily be compared. An international standard for low molecular weight heparin was established in 1986[4] and all manufacturers now use it to calibrate their products for both anti-Xa and anti-IIa activities. In some published and conference presentations, however, other units are still quoted. In particular, the Sanofi product, Fraxiparine, is often described in "Institut Choay Units" (ICU)—these being a measure of anti-Xa activity—but they should be divided by about 2·5 to obtain the equivalent in international units of anti-Xa activity. When this is done the dose requirement for prophylaxis of deep vein thrombosis in general surgery falls within a fairly narrow range for all products: from 2000 to 3500 IU of anti-Xa activity, once a day subcutaneously.

PHARMACOLOGY

Unfractionated heparin is available as sodium or calcium salt. After subcutaneous injection of equal amounts the overall anticoagulant activity is lower with calcium than with sodium salt, but this does not affect clinical efficacy. There may be a lower incidence of ecchymoses after subcutaneous injection of the calcium than of the sodium salt, but there is not clear evidence for any major differences in the incidence of haemorrhagic effects. All low molecular weight heparins are in the sodium form except Fraxiparine, which is a calcium salt.

Both unfractionated heparin and low molecular weight heparin are given parenterally, either by intravenous or subcutaneous injection. Metabolism is by a saturable mechanism, involving binding to endothelial cells and clearance by the reticuloendothelial system, and a non-saturable mechanism involv-

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ing mainly renal clearance. Both mechanisms are important for unfractionated heparin, but renal clearance predominates for low molecular weight heparin. There is no evidence that either unfractionated heparin or low molecular weight heparin crosses the placenta.

DIFFERENCES BETWEEN UNFRACTIONATED HEPARIN AND LOW MOLECULAR WEIGHT HEPARIN

The principal aspects in which low molecular weight heparin differs from unfractionated heparin are as follows:

Pharmacokinetics

Low molecular weight heparin has a longer half-life than unfractionated heparin, by both intravenous and subcutaneous injection.[5,6] The intravenous half-life is about 2 hours, measured as anti-Xa activity, though somewhat shorter (about 80 minutes) when measured by anti-IIa assay. The half-life of unfractionated heparin is dose-dependent but at normal intravenous doses is from 45–60 minutes by both assay methods. The subcutaneous half-life of low molecular weight heparin is about 4 hours, measured as anti-Xa activity. Unlike unfractionated heparin, which has a bioavailability of less than 50%, all low molecular weight heparins have a bioavailability after subcutaneous injection of 100%. These differences in pharmacokinetics and bioavailability are responsible for the successful use of once daily subcutaneous injections of low molecular weight heparin for prophylaxis of deep vein thrombosis. There is no evidence for differences in pharmacokinetics between the different products.

Interaction with proteins

Several proteins interact strongly with heparin to antagonise its anticoagulant activity, the most important being platelet factor 4 (PF4) and protamine. Binding affinity to these proteins is reduced with decreasing molecular weight, so that low molecular weight heparin preparations require higher concentrations of PF4 or protamine to neutralise their activity than does unfractionated heparin. Below 18 saccharides heparin chains become increasingly resistant to neutralisation by either of these agents, so that all low molecular weight heparin preparations have a portion of their anti-Xa activity which is non-neutralisable.[3,7] Animal studies indicate, however, that this does not affect the ability of protamine to neutralise the haemorrhagic action of low molecular weight heparins.[8]

Interaction with cells

Low molecular weight heparin binds less strongly than unfractionated heparin to endothelial cells, and this is partly responsible for the difference in pharmacokinetics, because endothelial binding and processing is an important mechanism of clearance for unfractionated heparin. Low molecular weight heparin also interacts with platelets less readily than unfractionated heparin, whether measured as potentiation of spontaneous aggregation or inhibition of agonist induced aggregation.[9]

Release of lipase

Low molecular weight heparin, when given in similar doses to unfractionated heparin, releases lower concentrations of the enzymes lipoprotein lipase and hepatic lipase from the vascular endothelium.

Clinical use of heparin

Heparin is used in the treatment of established thromboembolic disease (therapeutic administration) and to prevent thrombosis and embolism (prophylactic administration). It is also valuable in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Therapeutic administration

INDICATIONS

Therapeutic heparin is given to treat conditions in which thrombosis or embolism has occurred. More heparin is required for this purpose than for prophylaxis.

Currently accepted indications are: deep vein thrombosis; pulmonary embolism; myocardial infarction; unstable angina pectoris; acute peripheral arterial occlusion.

At present only unfractionated heparin can be recommended for therapeutic use in normal circumstances, although clinical trials of low molecular weight heparin are being conducted and already indicate a potential role in the outpatient management of deep vein thrombosis.[10,11]

Where possible, a coagulation screen and platelet count should be performed before beginning treatment.

ROUTE

Heparin can be given either intravenously by continuous infusion, using an infusion pump, or by intermittent subcutaneous injection into the anterior or anterolateral wall of the abdomen near the iliac crest or thigh, using small volume syringes with small bore needles so that a precise dose can be delivered.[12] The recommended concentration for subcutaneous administration is 25 000 IU/ml.

DOSAGE

Deep vein thrombosis and pulmonary embolism

In adults an intravenous loading does of 5000 IU is given, save in severe pulmonary embolism when 10 000 IU may be advisable. Anticoagulation is maintained by intravenous infusion of 1–2000 IU/hour or subcutaneous injection of 15 000 IU 12 hourly, adjusted in each case by laboratory monitoring, 4–6 hours after the treatment has started.

Children or small adults should receive a lower loading dose and maintenance therapy can be calculated on the basis of 15–25 IU/kg/hour intravenously or 250 IU/kg 12 hourly subcutaneously.

Myocardial infarction
Heparin is used to prevent:
(a) *Coronary reocclusion after thrombolysis* Current regimens include (i) 2000 IU intravenously followed by 12 500 IU subcutaneously 12 hourly after streptokinase,[13 14] (ii) 5000 IU followed by 1000 IU/hour intravenously after tissue plasminogen activator.[15]
(b) *Mural thrombosis* Subcutaneous injection of 12 500 IU subcutaneously 12 hourly for at least 10 days is effective.[13 16]

Unstable angina pectoris
An intravenous regimen is used. The same doses as for deep venous thrombosis and pulmonary emobolism given above apply.[17]

Acute peripheral arterial occlusion
Surgical treatment is often used in this condition and thrombolytic treatment or full therapeutic heparin treatment, or both, are frequently used.

Disseminated intravascular coagulation (DIC)
The use of heparin in DIC is not established but its use is logical where the manifestations are predominantly vaso-occlusive. Because of the risk of bleeding, it is unusual to administer more than 1000 IU/hour.

LABORATORY MONITORING
Daily laboratory monitoring is essential when therapeutic heparin is prescribed. The APTT technique is the most widely used for this purpose and a value of 1·5–2·5 times the midpoint of the normal range is common practice. Depending on the APTT reagents used, this roughly corresponds to a heparin concentration of 0·2–0·4 IU/ml.[18] The calcium thrombin time is an alternative test. The APTT and calcium thrombin time are not sensitive to low molecular weight heparin and are inappropriate for monitoring treatment with this drug.

ADJUSTMENT OF DOSE
Routine APTT tests should be performed at the same time each day and in the same relationship to subcutaneous doses. An interval of 4–6 hours between injection and testing is appropriate. An increased dose may require a small bolus injection of 3–5000 IU if an immediate effect is desired. If a reduction of dose is necessary it is advisable to stop the intravenous infusion for 30–60 minutes before reducing the dosage.

Where necessary, protamine can be given intravenously to neutralise the effect of heparin. The effect is instantaneous and 1 mg of protamine is roughly equivalent to 100 units of heparin. If heparin neutralisation is required 60 minutes after heparin injection only 50% of the theoretical calculated dose of protamine should be given, while after 2 hours from heparin injection only 25% of the calculated dose is appropriate. Dose can also be calculated by a protamine neutralisation test. Protamine should be given slowly over 10 minutes because it can cause hypotension and bradycardia, and not more than 40 mg of protamine should be given in any one injection except in the context of cardiopulmonary by pass. Treatment may have to be repeated because protamine is cleared from the circulation more rapidly than heparin. Allergic and even anaphylactic reactions may occur, particularly in diabetics who have received protamine zinc insulin.

DURATION OF TREATMENT
Parenteral treatment should continue until it is no longer required or until oral anticoagulants have achieved a therapeutic effect. This generally takes at least three days even if the INR falls within the appropriate therapeutic range earlier because of the different half-lives of the vitamin K dependent factors. Four to five days of heparin treatment is usually sufficient, but longer courses of nine to 10 days may be advisable for patients with massive ilio-femoral thrombosis or major pulmonary embolism.[19 20]

CONTRAINDICATIONS
There are no absolute contraindications to heparin but the main risk is abnormal bleeding.

Full treatment is more hazardous after major trauma or recent surgery (especially to the eye or nervous system).

It is not desirable to treat patients who are severely thrombocytopenic with heparin because the drug itself can reduce the platelet count (see complications) and because of the additional haemostatic defect. If it is necessary to give heparin to patients with thrombocytopenia a reduced loading and maintenance dose should be given.

Other relative contraindications include: congenital or acquired haemorrhagic diatheses; recent cerebral haemorrhage; uncontrolled hypertension; hepatic dysfunction including oesophageal varices; renal failure; peptic ulceration; known hypersensitivity to heparin.

Prophylactic administration

INDICATIONS
Prophylactic heparin is given to prevent deep venous thrombosis and pulmonary embolism, particularly in patients at risk when undergoing a surgical procedure under general anaesthesia which lasts for over 30 minutes and requires a stay in hospital after surgery.

In the context of general surgery high risk patients include those aged over 40, those who are obese, those who have a malignancy, those who have had prior deep vein thrombosis or pulmonary embolism, those with an established thrombophilic disorder and those undergoing large or complicated surgical procedures. Any patient undergoing major orthopaedic surgery has a higher risk of thromboembolism and special techniques have been developed to address this problem. The prevention of deep vein thrombosis and pulmonary embolism in these and other situations was the subject of a consensus conference held by the US National Institutes of

Health in 1986.[21] This remains a useful source of information and advice, although low molecular weight heparin was not available at that time. It also contains a valuable review of the indications for other methods of prophylaxis such as low dose warfarin, dextran, external pneumatic compression and graduated-compression elastic stockings. A more recent account of the prophylaxis of deep vein thrombosis has been published.[22]

General surgery

The recommended regimen for general surgery using unfractionated heparin is[23]:

Preoperative 2 hours—5000 IU subcutaneously
Postoperative —5000 IU subcutaneously every 8–12 hours for 7 days or until patient is mobile.

Low molecular weight heparins have not been shown to be more effective than unfractionated heparin in this group. There is no consistent evidence of a clinically important alteration in postoperative bleeding.[24]

Dose requirements for each product have been established following extensive clinical trials, and manufacturers' dose recommendations should be strictly followed. It should be noted that overdosage with low molecular weight heparins may cause bleeding without a significant prolongation of the APTT.

No laboratory monitoring is necessary for standard prophylactic doses of unfractionated heparin or low molecular weight heparins. If it is decided that monitoring of prophylactic heparin is desirable then anti-Xa assays should be used. These assays may be performed by coagulation methods but are simpler by chromogenic substrate techniques, and commercial assay kits are available. Both methods should be controlled by the appropriate international heparin standard. In the event of overdose it may be more difficult to neutralise the effect of low molecular weight heparin because of its longer half-life and lesser sensitivity to protamine.

Orthopaedic surgery

Standard heparin prophylaxis can reduce the risk of thromboembolism in patients undergoing major orthopaedic procedures but despite its use 25% of patients will still develop deep vein thrombosis.[25] Several solutions have been proposed.

Adjusted dose heparin—A dose adjusted regimen using APTT monitoring to maintain minimal prolongation of the test has been shown to reduce further the incidence of thrombosis in hip surgery.[26,27] This approach requires close cooperation between surgical and laboratory staff.

Low molecular weight heparin—Several studies have shown that low molecular weight heparin in a fixed dose can reduce the incidence of venous thrombosis to about 15%.[24]

Turpie *et al* conducted a randomised trial of enoxaparin compared with placebo in patients undergoing total hip replacement using a fixed dose regimen and showed a fourfold reduction in thrombosis.[28] The overall incidence of venous thrombosis in the treated group was 12% with a 4% incidence of proximal thrombosis. There was no evidence of an increase in bleeding. Leyvraz *et al* compared their adjusted dose unfractionated heparin regimen with a fixed dose of Fraxiparine and showed that the low molecular weight heparin was more effective in preventing proximal venous thrombosis after hip replacement, with comparable bleeding complications.[29]

Thus low molecular weight heparin seems to be the treatment of choice in major orthopaedic surgery to the lower limb because of its effectiveness and because the once daily regimen requires no laboratory monitoring.

Warfarin prophylaxis—Although this is effective, some surgeons are reluctant to operate on patients taking warfarin.

Heparin plus dihydroergotamine—Dihydroergotamine 0·5 mg subcutenously is given with each standard heparin dose.[30] The disadvantage of this approach is the risk of peripheral ischaemia.

OTHER PREPARATIONS

Several other preparations are being developed which may have a role in the prevention of venous thromboembolism. Of these, dermatan sulphate, heparan sulphate, and the low molecular weight heparinoids are related to heparin and have been considered by Samama and Desnoyers.[24]

Pregnancy

Heparin is the drug of choice for women who require anticoagulation during pregnancy because it does not cross the placenta. It does carry the risk of causing maternal osteoporosis, however, particularly if the dose exceeds 20 000 IU/24 hours for more than 5 months.[18] There are no conclusive scientific data on this subject and information is often contradictory. Dahlman, Lindvall, and Hellgren found no correlation between osteoporosis and heparin dose or duration of treatment in pregnancy, and in their study the changes were reversible in most cases,[31] findings which contrast with those of the earlier study by de Swiet *et al.*[32] It should be remembered that oral anticoagulation can be reintroduced immediately after delivery where necessary and that women taking warfarin may safely breastfeed.

PROPHYLAXIS OF THROMBOEMBOLISM

To prevent thromboembolism in mothers with a history of deep vein thrombosis or pulmonary embolism an initial dose of 5000 IU 12 hourly by self administered subcutaneous injection has been recommended. An increase in dose may be needed in the last trimester to prolong the APTT to 1·5 times an average control value at the midinterval[22] although this can be difficult to achieve. Letsky recommends 10 000 IU 12 hourly subcutaneously throughout the antenatal period, only changing the dose by reducing it if levels of more

than 0·3 IU/ml are found by anti-Xa assay.[33] Titrated heparin has been used successfully in the management of antithrombin III deficiency, antithrombin III concentrate being used to cover delivery.[34] Some authorities caution against the prescription of warfarin at any stage of pregnancy because of the risk of embryopathy in the first trimester and fetal haemorrhage later, but others approve its use from 16–36 weeks, maintaining the INR between 2·0–3·0. The exact time at which any prophylaxis is started will depend on the nature of the risk, the previous obstetric history, and the mother's own wishes but it may be possible to delay drug treatment until late in pregnancy when the greatest risk of thromboembolism develops.

Patients receiving full therapeutic doses of heparin must reduce their heparin dose on the day of delivery to a dose of 10 000–15 000 IU/24 hours intravenously (or 5000–7500 12 hourly subcutaneously). Patients receiving prophylactic doses of heparin should generally continue their treatment unchanged during labour and delivery. In any event the APTT must be checked to ensure that anticoagulation is not excessive.

Epidural analgesia for those women who have been receiving heparin during pregnancy remains a difficult and controversial problem, but providing the coagulation screen is within normal limits it is probably safe to introduce an epidural catheter.[35]

ANTIPHOSPHOLIPID SYNDROMES

Patients with lupus anticoagulant or anticardiolipin antibodies, or both, who have experienced previous thrombotic episodes should also receive heparin prophylaxis. Where patients have suffered recurrent miscarriages despite low dose aspirin treatment, heparin prophylaxis should be considered in subsequent pregnancies. If heparin monitoring is performed the APTT test may be unreliable and an anti-Xa assay is better.

PROSTHETIC HEART VALVES

The management of pregnant women with prosthetic heart valves is difficult and controversial. The problems have been highlighted by Iturbe-Alessio *et al.*[36] They found that low dose heparin 5000 IU 12 hourly subcutaneously was ineffective in preventing valve thrombosis while the incidence of embryopathy in patients receiving coumarin derivatives from the 6th to the 12th week of gestation was between 25 and 30%. A higher dose of heparin (15 000 IU 12 hourly subcutaneously) has been recommended by Hirsh.[18] Women with artificial heart valves who wish to become pregnant therefore require careful counselling. It is important to emphasise that there is no perfect solution to the problem and that the choices of management will lie between:

(i) Continuing warfarin throughout pregnancy and accepting the risk of embryopathy.

(ii) Using heparin throughout pregnancy and accepting the risk of osteoporosis as well as a possible increased risk of thrombosis.

(iii) Using heparin until 12–16 weeks, followed by warfarin up to 36 weeks, and then reverting to heparin until delivery.

When using the higher dose heparin prophylaxis it would be wise to monitor APTT, aiming to achieve values about 1·5 times an average control value at the mid interval.

LOW MOLECULAR WEIGHT HEPARIN

It is still too early to give any specific recommendations on these preparations in pregnancy. They have the advantage of once daily administration but there is no reason to believe that osteoporosis will be less likely to occur with prolonged use.

In circumstances where higher doses are required anti-Xa assays are necessary for laboratory monitoring.

Extracorporeal circulation and haemodialysis

CARDIOPULMONARY BYPASS

Heparin is universally used as the anticoagulant during cardiopulmonary bypass procedures.

The bypass machine is primed with a crystalloid solution to which 1000 IU of heparin are added to each 500 ml. If stored blood is also used for priming 3000 IU are added to each unit of blood.

Before the cannulation of the heart and major blood vessels, which is required before bypass surgery can begin, heparin is given intravenously through a cannula placed in a large central vein. The dose is determined on the basis of the surface area or weight of the patient. Usually the initial dose is 300 IU/kg.

The administration of heparin is controlled both before, during, and after bypass by monitoring the activated clotting time (ACT) in an automated system in the operating theatre. Estimations are made every 30 minutes. In patients not receiving heparin the normal ACT in one system is 100–140 seconds. During cardiopulmonary bypass the safe range is between 400–500 seconds and further increments of 5000 IU are given to maintain this level, as necessary.[37]

When bypass is discontinued heparin can be reversed readily with protamine. A standard dose is usually given, but it is more sophisticated, though more time consuming, to titrate the dose of protamine with ACT measurements using ACT tubes to which known amounts of protamine have been added.[38]

Protamine, unlike heparin, may have toxic effects on the cardiopulmonary circulation and it is usual to adminster protamine cautiously after bypass.

HAEMODIALYSIS AND HAEMOFILTRATION

None of the membranes used in haemodialysis and haemofiltration is sufficiently biocompatible to enable the dialysis process to be carried out without anticoagulation of the circuit. In modern haemodialysis machines a heparin pump is incorporated and heparin is infused directly into the exit line of the extra-

corporeal circuit. Current clinical practice is to administer a loading dose of heparin at the start of the session, and to give a continuous infusion, which is usually discontinued about one hour before dialysis is due to stop to allow adequate haemostasis to take place when the dialysis needles are removed.

The dose requirements of the patients receiving dialysis vary widely according to the individual. The anticoagulant effect is usually monitored by whole blood clotting time and, in patients without potential bleeding complications, the clotting time is usually maintained in excess of 40 minutes. In practice, to achieve this will require a loading dose which varies from 1–5000 IU and a maintenance dose of 1–2000 IU hour which gives a heparin concentration of > 0·5 IU/ml.[39] The dose variability depends on the weight of the patient, the volume of the extracorporeal circuit, the pump speed, which can vary from 150–450 ml/minute, and the biocompatibility of the dialysis membrane. In patients who are actively bleeding, or who have a known bleeding tendency it is possible to dialyse for short periods without heparin, using high pump speeds and short dialysis circuits. Usually, however, lines will begin to clot between 60 and 120 minutes after starting dialysis. Alternatively, regional heparin treatment can be given; heparin is infused into the circuit as the blood leaves the patient and a neutralising dose of protamine is infused into the circuit as the blood is returned to the patient.

Low molecular weight heparins

A potential advance in this area has been the introduction of low molecular weight heparins which have a much prolonged half-life in renal failure and therefore may have the advantage of avoiding maintenance infusion. Lipolytic effects tend to be less. Interestingly, patients receiving maintenance haemodialysis will be anticoagulated with heparin for about 900 hours a year and the question of whether heparin induces osteoporosis has been much discussed. This bony lesion has been very difficult to extrapolate from the complex picture of renal osteodystrophy, however, and there is no hard evidence that it is a major clinical problem or that low molecular weight heparins will be less likely to contribute to it.

Monitoring of low molecular weight heparins in haemodialysis by anti-Xa assays is still not fully established, although the low molecular weight international standard will be useful, and the new technique has not yet achieved wide acceptance.

Complications

HAEMORRHAGE

Haemorrhage usually results from excess dose or idiosyncratic response to conventional dose. Serious concurrent illness, chronic heavy consumption of alcohol, and concomitant use of aspirin have also been implicated.[18]

The management of heparin overdose has already been considered in the section on adjustment of dosage.

THROMBOCYTOPENIA

This is a rare complication of heparin treatment in the United Kingdom and may be commoner with the bovine then the porcine preparation. It can occur at any dose and whether heparin is given by the intravenous or subcutaneous route. Both unfractionated heparin and low molecular weight heparin are associated with thrombocytopenia and regular monitoring of the platelet count is advisable.

Clinically important thrombocytopenia is usually delayed, occurring 6–10 days after the start of treatment and is immune mediated. Paradoxical thrombosis is common and the heparin should be stopped immediately.[18]

Heparin from a different source or low molecular weight heparin may be tried but cross-reactivity has been described and it is difficult to judge the appropriate dose of low molecular weight heparin for therapeutic use. The heparinoid ORG 10172 has minimal cross-reactivity with heparin. Hirudin and ancrod are other potential alternative drugs.

An immediate decline in the platelet count after starting therapy is also occasionally observed, and is thought to be a direct effect due to platelet aggregation and probably does not occur with low molecular weight heparin. It is of little clinical importance.

OSTEOPOROSIS

This complication of heparin treatment has only been described with prolonged use and is probably independent of molecular size. It is discussed in the section on pregnancy.

ABNORMAL LIVER FUNCTION TESTS

An increase in serum aminotransferase activity has been reported in patients who are being treated with heparin. This does not seem to be of any clinical importance.[40]

OTHER SIDE EFFECTS

Localised skin necrosis and anaphylaxis caused by hypersensitivity have been described. Alopecia is very rare.

Medical audit

The use and monitoring of heparin treatment is a suitable topic for medical audit which might include local reviews of indications, therapeutic and prophylactic doses, and control.

Protocols might be drawn up for the use of heparin in pregnancy and agreement reached on the indications for the various heparin preparations available.

These guidelines should be read in conjunction with Guidelines on oral anticoagulation: second edition 1990[1] and Guidelines on the prevention, investigation, and management of thromboembolism in pregnancy 1992 (to be published) which have also been prepared by the Task Force.

The advice contained in these guidelines is believed to represent the state of the art at the time of going to press. It is policy to revise the guidelines as new developments occur. It may not be possible to do this at the time of such changes,

however, and the guidelines should always be used with due regard to current acceptable practice.

Comments are invited to assist the review process.

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