LEO-Heparin

Heparin is indicated for prophylaxis and treatment of venous thrombosis and pulmonary embolism; in the treatment of myocardial infarction and arterial embolism; for prevention of clotting in arterial and heart surgery and for prevention of cerebral thrombosis. Heparin may also be used as an anticoagulant in blood transfusions, extra-corporal circulation, dialysis procedures, and for laboratory purposes.

**Administration**

Heparin is usually administered by intravenous or subcutaneous injection. The intramuscular route cannot be recommended because of the high incidence of haematoma.

The increase in clotting time provided by heparin becomes apparent immediately after administration and lasts for 4 to 6 hours after intravenous injection and for about eight hours after subcutaneous injection.

**Dosage**

Haemodialysis: 7,500–12,500 i.u. is normally required per dialysis. Intravenous administration: 5,000–10,000 i.u. every four hours either by bolus injection or continuous infusion in Sodium Chloride Injection or Dextrose Injection. However, the dose should be monitored with coagulation tests performed just before each administration and varied according to individual response. The clotting time should be 2–3 times the control value.

Subcutaneous administration (Therapeutic dosage): Subcutaneous administration of 10,000 i.u. may be given every 8 hours after an initial intravenous bolus injection of 5,000 i.u.

Low-dose heparin prophylaxis: 5,000 i.u. in 0.2 ml s.c. should be given two to six hours pre-operatively and every 8–12 hours post-operatively for 10–14 days, or until the patient is mobile, which ever is the longer.

Myocardial infarction: 5,000 i.u. s.c. every twelve hours beginning during the twelve hours following the first sign of myocardial infarction.

Open heart surgery: Operations of less than two
hours, 120 i.u./kg/hour. For operations of longer
duration, one and a half times this dose should be
given. For each 450 ml of blood used, 2,000 i.u. are
needed.
Treatment periods vary from 10–14 days in peri-
operative prophylaxis to as much as six weeks in
the treatment of established thrombosis.
It is anticipated that heparin will have disappeared
from the blood-stream 4 hours after intravenous
injection of 5,000 i.u and 6–8 hours after 10,000 i.u.
and 15,000 i.u. of i.v. heparin, respectively.
In situations needing large amounts of heparin, as in
cardio-pulmonary bypass, preservative-free heparin
should be used. If this is unavailable and preserved
heparin has to be used, then the most concentrated
heparin solution (25,000 IU/ml) should be chosen to
minimise the quantity of preservative administered.

Pregnancy
The antithrombotic drug of choice during pregnancy
should be heparin, even taking into consideration
the fact that longterm (6 months or more) applica-
tion of heparin can cause severe osteoporosis in the
mother. To minimize the risk of osteoporosis heparin
is given in the first trimester, followed by coumarin
therapy until about the 36th week, and then hepa-
rin is given for the last few weeks. Heparin therapy
should be completely stopped six hours before
delivery.

Contraindications
Heparin is contraindicated in patients known to
have hypersensitivity to heparin. It is also contrain-
dicated when suitable blood coagulation tests – e.g.
the whole-blood clotting time, partial thromboplastin
time, – cannot be performed at the required inter-
vals. There is usually no need to monitor the effect
of low-dose heparin in patients with normal coagu-
lation parameters. The drug is contraindicated dur-
ing any uncontrolled active bleeding state (see
Warnings).
Heparin without preservatives should be used in
premature infants.

Side-effects
Transient alopecia and diarrhoea may occur.
Thrombocytopenia and osteoporosis with spontane-
ous fractures have been reported. Febrile or allergic
reactions have occasionally been reported.

Warnings
When heparin sodium is administered in therapeu-
tic amounts, its dosage should be regulated by fre-
quent blood coagulation tests. If the coagulation test
is unduly prolonged or if haemorrhage occurs hepa-
rin sodium should be discontinued promptly (See
Overdosage).
Some of the conditions in which increased danger of
haemorrhage exists are as follows:
Cardiovascular – Subacute bacterial endocarditis;
arterial sclerosis; increased capillary permeability;
during and immediately following (a) spinal tap or
spinal anaesthesia or (b) major surgery, especially
involving the brain, spinal cord or eye.
Haematologic – Conditions associated with
increased bleeding tendencies, such as haemophil-
ia, some purpuras, and thrombocytopenia.
Gastro-intestinal – Inaccessible ulcerative lesions
and continuous tube drainage of the stomach or
small intestine.
Heparin may prolong the one-stage prothrom-
bin time. Therefore, when heparin sodium is given
with dicumarol or warfarin sodium, a period of at
least five hours after the last intravenous dose or
24 hours after the last subcutaneous dose should
elapse before blood is drawn if a valid prothrombin
time is to be obtained.

Overdosage
Bleeding may be a complication of therapy.
Slight epistaxis, occasional red cells in the urine,
and bruising are signs of overdosage.
Slight haemorrhage due to overdosage can usually
be treated by withdrawing the drug. Severe bleeding
may be reduced by the administration of protamine
sulphate.
The effect of heparin can be reversed immediately
by intravenous administration of 1% protamine sul-
phate solution.
The injection should be given very slowly (over
one to three minutes). The quantity of protamine
required for neutralization falls rapidly with the lapse
of time after the administration of heparin. If given
Digitalis, tetracycline, nicotine, or antihistamines may partially counteract the anticoagulant action of heparin sodium. An increased resistance to the drug is frequently encountered in thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, and postsurgical patients.

Package sizes: 5,000 IU/ml: 5 ml x 50, 5 ml x 5
1,000 IU/ml: 5 ml x 50, 5 ml x 5

**Shelf life**
3 years

within 15 minutes of the heparin injection 10 mg of protamine will neutralize 1,000 i.u. of heparin, while 30 minutes after the heparin injection of 1,000 i.u., only 5 mg of protamine sulphate is needed. If more time has elapsed after the administration of heparin, the dose of protamine sulphate required for neutralization should be determined accurately by titrating with the patient’s plasma.

It is important to avoid overdosage of protamine sulphate because protamine itself has anticoagulant properties. The dosage should not exceed the equivalent of 50 mg protamine sulphate in any ten-minute period. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea, and transitory flushing, but these may be avoided or diminished by slow administration.

**Storage Conditions**
Do not store above 30°C
In-use period: 28 days when stored below 25°C.

**Precautions**
Heparin therapy should be given with caution to patients about to undergo surgery, and those with impaired renal or hepatic function.

If oral anticoagulants are started, heparin should be continued in slightly decreasing doses for another 4–5 days until the oral drug has attained full prothrombin depressing activity.

Heparin should be used with caution in any patient with a history of allergy. Before a therapeutic dose is given to such a patient, a trial dose of 1,000 units may be advisable.

**Dosage in the elderly**
Elderly women have a greater tendency to bleed and it may be necessary to reduce the dose according to coagulation tests, but dosage alterations are unlikely for prophylaxis.

**Interactions**
Drugs (such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, and hydroxychloroquine) that interfere with platelet-aggregation reactions may induce bleeding and should be used with caution in patients receiving heparin. It may be necessary to increase doses of heparin in the febrile state.