HEPARON

Heparin Sodium

COMPOSITION

Heparon Injection: Each 5 ml contains Heparin Sodium BP 25,000 IU.

DESCRIPTION

HEPARIN SODIUM intravenous infusion is a sterile, nonpyrogenic solution of Heparin Sodium (BP) standardised for use as an anticoagulant.

Heparin is a heterogenous mixture of variably sulphated polysaccharide chains composed of repeating units of disaccharides, D-glucosamine and L-iduronic acid or D-glucosamine and D-glucuronic acids. It is extracted from porcine intestinal mucosa. Upon complete hydrolysis, it yields a mixture of D-glucosamine, D-glucuronic acid, L-iduronic acid, acetic acid and sulphuric acid. Heparin is strongly acidic because of its content of covalently linked sulphate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulphate units are partially replaced by sodium ions.

Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) β-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2) > (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes.

CLINICAL PHARMACOLOGY

Mechanism of Action

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with Antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilising factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases it is not measurably affected by low doses of heparin.

Heparin does not have fibrinolytic activity; therefore it will not lyse existing clots.

Clinical trials have not demonstrated the superiority of heparin in the maintenance of catheter patency over fluid not containing anticoagulant medication (eg. normal saline).

INDICATIONS

HEPARIN SODIUM Injection is indicated as an anticoagulant in extracorporeal circulation, dialysis procedures, and as an aid in the maintenance of catheter patency.

DOSAGE AND ADMINISTRATION

Administer Heparin Sodium Injection by Intermittent IV Injection, IV Infusion, or Deep Subcutaneous Injection. Heparin Sodium Injection is not intended for Intramuscular (IM) use.

HEPARIN SODIUM is not effective by oral administration and should not be given orally.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Use of a final filter is recommended during administration of all parenteral solutions, where possible.

Deep Subcutaneous (Intrafat) Injection	Initial Dose	333 units/kg subcutaneously
Use a different site for each injection	Every 12 hours	250 units/kg subcutaneously
Intermittent	Initial Dose	10,000 units
IV Injection	Every 4 to 6 hours	5,000 to 10,000 units
Continuous	Initial Dose	5,000 units
IV Infusion	Continuous	20,000 to 40,000 units/24 hours

Use in Extracorporeal Therapy

The concentration of 2 units/mL will suffice to prevent clotting on initiation of extracorporeal therapy by priming the devices with this solution. NOTE: A proper and effective heparinisation schedule must be initiated in the patient before and maintained throughout the procedures to prevent subsequent clotting and blood path obstruction. The particular manufacturer's directions for use of the dialyser or other extracorporeal apparatus must be referred to. The direction sheets for the use of therapeutic dosage forms of heparin must equally be referred to and adjusted to a given patients condition and response to achieve sustained, effective anticoagulation within clinically safe parameters. Both intermittent and continuous infusion of 5000, 10000 or 20000 units are employed for this purpose and are unrelated to the low dose heparin in this preparation that is directed at preparing the apparatus for initial use.

Maintenance of Catheter Patency

Although the rate for infusion of the 2 units/mL formulation is dependent upon age, weight, clinical condition of the patient and the procedure being employed, an infusion rate of 3 mL/hour has been found to be satisfactory.

Periodic platelet counts; hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

Because dosages of this drug are titrated to response, no additives should be made to HEPARIN SODIUM Injection.

CONTRAINDICATIONS

HEPARIN SODIUM should not be used in the following patients:

With severe thrombocytopenia; In whom suitable blood coagulation tests - e.g., the whole-blood clotting time, partial thromboplastin time etc - cannot be performed at appropriate intervals (this contraindication refers to full-dose heparin; there is usually no need to monitor coagulation parameters in patients receiving low dose heparin);

With an uncontrollable active bleeding state, except when this is due to disseminated intravascular coagulation.

PRECAUSIONS

General

White Clot Syndrome

It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so-called "white clot syndrome". The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possible death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

Spinal/Epidural Haematomas

When neuraxial anaesthesia (epidural/spinal anaesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with unfractionated heparin or low molecular weight heparins/heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDS), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patient's anticoagulated or to be anticoagulated for thromboprophylaxis.

Heparin Resistance

Haemorrhage: Haemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of hemorrhagic event.

HEPARIN SODIUM should be used with extreme caution in disease states in which there is increased danger of haemorrhage. Some of the conditions in which increased danger of haemorrhage exists are:

Cardiovascular - Subacute bacterial endocarditis. Severe hypertension.

Surgical - During and immediately following (a) spinal tap or spinal anaesthesia or (b) major surgery, especially involving the brain, spinal chord or eye.

Haemotologic-Conditions associated with increased bleeding tendencies, such as haemophilia, thrombocytopenia, and some vascular purpuras.

Gastrointestinal-Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other - Menstruation, liver disease with impaired hemostasis.

Coagulation Testing

When HEPARIN SODIUM is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if haemorrhage occurs, HEPARIN SODIUM should be discontinued promptly.

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Mild thrombocytopenia (count greater than 100,000/mm3) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm3 or if recurrent thrombosis develops, the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.

Solutions containing sodium ions should be used with great care in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists oedema with sodium retention.

The intravenous administration of solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, over hydration, congested states or pulmonary oedema. The risk of dilutional states is inversely proportional to the electrolyte concentrations and volume of the infusion. The risk of solute overload causing congested states with peripheral and pulmonary oedema is directly proportional to the electrolyte concentrations and volume of the infusion.

Excessive administration of potassium free solutions may result in significant hypokalaemia.

In patients with diminished renal function, administration may result in sodium retention.

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thromocytopenia and Thrombosis (HITT).

Heparin-induced Thrombocytopenia (HIT) is a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to the development of venous and arterial thromboses, a condition referred to as Heparin-induced Thrombocytopenia and Thrombosis (HITT). Thrombotic events may also be the initial presentation of HITT. These serious thromboembolic events include deep vein thrombosis, pulmonary embolism, cerebral vein thrombosis, limb ischemia, stroke, myocardial infarction, mesenteric thrombosis, renal arterial thrombosis, skin necrosis, gangrene of the extremities that may lead to amputation, and possibly death.

Thrombocytopenia of any degree should be monitored closely. If the platelet counts fall below 100,000/mm3 or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulant considered if patients require continued anticoagulation.

Delayed Onset of HIT and HITT

Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis can occur up to several weeks after the discontinuation of heparin therapy. Patients presenting with thrombocytopenia or thrombosis after discontinuation of heparin should be evaluated for HIT and HITT.

Laboratory Tests

Periodic platelet counts; hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration (see Dosage and Administration).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

Use in Pregnancy (Category C)

Heparin does not cross the placental barrier. Animal reproduction studies have not been conducted with HEPARIN SODIUM. It is not known whether HEPARIN SODIUM can cause foetal harm when administered to a pregnant woman or can affect reproduction capacity. HEPARIN SODIUM should be given to pregnant women only if clearly needed.

Use in Lactation

Heparin Sodium is not excreted in human milk.

Paediatric Use

Safety and effectiveness in paediatric patients has not been established.

SIDE EFFECTS

1. Haemorrhage

Haemorrhage is the chief complication that may result from heparin therapy (see Warnings and Precautions). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see Overdosage). It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific haemorrhage complications may be difficult to detect:

a. Adrenal haemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal haemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in a patient's death.

b. Ovarian (corpus luteum) haemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication, if unrecognised, may be fatal.

c. Retroperitoneal haemorrhage.

2. Local Irritation

Local irritation, erythema, mild pain, haematoma or ulceration may follow deep subcutaneous (intrafat) injection of HEPARIN SODIUM. These complications are much more common after intramuscular use, and such use is not recommended.

3. Hypersensitivity

General hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar site of the feet, may occur.

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 - 30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke and possible death.

Certain episodes of painful, ischaemic, and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia-associated complications remains to be determined.

4. Miscellaneous

Osteoporosis following long term administration of high doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported. Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.

OVERDOSE

Symptoms

Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

Treatment

Neutralization of heparin effect

When clinical circumstances (bleeding) require reversal of heparinisation, protamine sulphate (1% solution) by slow infusion will neutralise HEPARIN SODIUM. No more than 50mg should be administered, very slowly in any 10-minute period. Each mg of protamine sulphate neutralises approximately 100 BP heparin units. The amount of protamine required decreases over time as heparin is metabolised. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about ½ hour after intravenous injection.

Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.

For additional information the labelling of Protamine Sulphate Injection, USP products should be consulted.

DRUG INTERACTIONS

Oral anticoagulants

HEPARIN SODIUM may prolong the one-stage prothrombin time. Therefore when HEPARIN SODIUM is given with dicumarol or warfarin sodium, a period of at least 5 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.

Platelet Inhibitors

Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet aggregation reactions (the main hemostatic defence of heparinised patients) may induce bleeding and should be used with caution in patients receiving HEPARIN SODIUM.

Other Interactions

Digitalis, tetracyclines, nicotine, or antihistamines may partially counteract the anticoagulant action of HEPARIN SODIUM.

Drug/Laboratory Tests Interactions

Hyperaminotransferaemia

Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

PHARMACEUTICAL INFORMATION

Storage condition

Store the vial in original carton at 20°C to 25°C, away from light. Keep out of the reach of children.

Presentation and Packaging

Heparon Injection: Each commercial box contains 1 vial of 5 ml Heparin Sodium Injection (5,000 IU/ml).

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