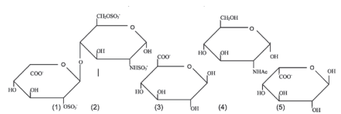
HEPARIN EP, LOCK FLUSH SOLUTION

DESCRIPTION

Heparin EP, Lock Flush Solution (preservative free) is a sterile solution for intravenous flush only. It is not to be used for anticoagulant therapy. It is specially formulated for use in newborns and in situations where the use of preservatives is not advisable. Each ml of the single dose (preservative free) preparation contains Heparin sodium Ph. Eur. 10 or 100 International units. and 9 mg sodium chloride in water for injection. The potency is determined by Ph. Eur. biological assay using the current WHO standard.

Heparin is a heterogeneous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans having anticoagulant properties. 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. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions.

Structure of Heparin Sodium (representative sub-units):



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 the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing 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.

INDICATIONS AND USAGE

Heparin Lock Flush Solution is intended to maintain patency of indwelling intravenous catheter designed for intermittent injection therapy or blood sampling.

Heparin Lock Flush Solution may be used following initial placement of the device in the vein, after each injection of a medication or after withdrawal of blood for laboratory analysis. See “Dosage and Administration” under Clearing intermittent infusion sets for directions for use.

Heparin Lock Flush Solution is not to be used for anticoagulant therapy.

CONTRAINDICATIONS

Hypersensitivity to heparin; severe thrombocytopenia. Heparin sodium should NOT be used in patients with an uncontrollable active bleeding state (see “Warnings”), except when this is due to disseminated intravascular coagulation.

WARNINGS

Heparin EP, Lock Flush Solution should be used with special caution in infants with disease states in which there is an increased danger of hemorrhage.

Hemorrhage 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. An overly prolonged clotting time or minor bleeding can usually be controlled by withdrawing the drug. Use heparin with extreme caution in disease states in which there is increased danger of hemorrhage. These include:

Cardiovascular – Subacute bacterial endocarditis; dissecting aneurysm; increased capillary permeability; severe hypertension.

CNS –During and immediately following spinal tap, spinal anesthesia or major surgery, especially of the brain, spinal cord or eye; suspected intracarnial hemorrhage.

Hematologic – Hemophilia; some vascular purpuras; thrombocytopenia.

GI – Ulcerative lesions, diverticulitis or ulcerative colitis; continuous tube drainage of the stomach or small intestine.

Obstetric – Threatened abortion; menstruation.

Other – Liver disease with impaired hemostasis; active tuberculosis; visceral carcinoma; alcohol abuse.

Heparin is not intended for intramuscular use.

Hypersensitivity – Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations. (See “Adverse Reactions”.)

Thrombocytopenia

Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Platelet counts should be obtained at baseline and periodically during heparin administration. Mild thrombocytopenia (count greater than 100,000/mm^3) 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/mm^3 or if recurrent thrombosis develops (see Heparin-induced Thrombocytopenia and Heparin-induced Thrombocytopenia and Thrombosis), the heparin product should be discontinued and, if necessary, an alternative anticoagulant administered.

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia 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 for 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 count falls below 100,000/mm^3 or if recurrent thrombosis develops, the heparin product should be promptly discontinued and alternative anticoagulants 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.

Use in Neonates and Infants

The 100 International unit/mL concentration should not be used in neonates or in infants who weigh less than 10 kg because of the risk of systemic anticoagulation. Caution is necessary when using the 10 International unit/mL concentration in premature infants who weigh less than 1 kg who are receiving frequent flushes since a therapeutic heparin dose may be given to the infant in a 24-hour period.

PRECAUTIONS

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT), see WARNINGS

Resistance – Increased resistance to the drug is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, MI, cancer and postoperative states.

Increased risk in older women – A higher incidence of bleeding has been reported in women over 60 years of age.

Laboratory tests - Periodic platelet count, hematocrit, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the rout of administration.

General – Precautions must be exercised with drugs which are incompatible with heparin or administered through an indwelling intravenous catheter containing Heparin Lock Flush Solution. (See “Dosage and Administration”.)

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

Pregnancy –

Teratogenic effects – Pregnancy Category C: Animal reproduction studies have not been conducted with heparin sodium. It is also not known whether heparin sodium can cause fetal harm when administered to pregnant woman

or can effect reproduction capacity. Heparin Sodium should be given to a pregnant woman only if clearly needed.
Non teratogenic effects: Heparin does not cross the placental barrier.
Nursing mothers – Heparin is not excreted in human milk.

DRUG INTERACTIONS

Platelet inhibition – Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet aggregation reactions (the main hemostatic defense of heparinized 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.

ADVERSE REACTIONS

Hemorrhage – Hemorrhage is the chief complication that may result from heparin. An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug. (See "Overdosage".)
Significant GI or urinary tract bleeding may indicate an underlying occult lesion. Bleeding can occur at any site. Certain hemorrhagic complications may be difficult to detect:

i. Adrenal hemorrhage resulting in acute adrenal insufficiency has occurred.
Discontinue therapy in patients who develop signs and symptoms of acute adrenal hemorrhage or insufficiency. Measure plasma cortisol levels and institute vigorous IV corticosteroid therapy. Initiation of therapy should not depend on laboratory confirmation of diagnosis, since any delay in an acute situation may result in the patient's death.
ii. Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving anticoagulants. This complication, if unrecognized, may be fatal.
iii. Retroperitoneal Hemorrhage.

Thrombocytopenia, Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis (HITT), see WARNINGS

Local – Avoid IM use. Local irritation, erythema, mild pain, hematoma or ulceration may follow deep SC use, but are more common after IM use. Histamine-like reactions and cutaneous necrosis have been observed.
Hypersensitivity – Generalized hypersensitivity reactions have been reported, with chills, fever and urticaria as the most usual manifestations, asthma, rhinitis, lacrimation, headache, nausea and vomiting, anaphylactoid reactions including shock, occurring more rarely. Itching and burning, especially on the plantar side 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 possibly death. (See "Warnings" and "Precautions".)
Certain episodes of painful, ischemic 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.
Other – Osteoporosis and function suppression after long-term high doses; cutaneous necrosis, suppressed aldosterone synthesis, delayed transient alopecia, priapism and rebound hyperlipemia after discontinuation.
Significant elevation 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.

OVERDOSAGE

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 heparinization, protamine sulfate by slow infusion will neutralize heparin sodium. No more than 50 mg should be administered, very slowly, in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 International units of heparin. The amount of protamine required decreases over time as heparin is metabolized. 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. Nevertheless, the

required protamine sulphate dose varies according to the time of heparin administration and dose administered.
It is important to avoid overdosage of protamine sulphate because protamine sulphate itself has anticoagulant properties.
Administration of protamine sulfate 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 consult the labeling of Protamine Sulfate Injection products.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Slight discoloration does not alter potency.
Clearing Intermittent Infusion (Heparin Lock) Sets – To prevent clot formation in a heparin lock set following its proper insertion, Heparin Lock Flush Solution is injected via the injection hub in a quantity sufficient to fill the entire set to the needle tip. This solution should be replaced each time the heparin lock is used. Aspirate before administration any solution via the lock in order to confirm patency and location of needle or catheter tip. If the drug to be administered is incompatible with heparin, the entire heparin lock set should be flushed with normal saline before and after the medication is administered; following the second flush, Heparin Lock Flush Solution may be re-instilled into the set. The set manufacturer's instructions should be consulted for specifics concerning the heparin lock set in use at a given time.
NOTE: Since repeated injections of small doses of heparin can alter tests for activated partial thromboplastin time (APTT), a baseline value for APTT should be obtained prior to insertion of a heparin lock set.
Usually these dilute heparin solutions will maintain anticoagulation within the device for up to four hours.
Withdrawal of blood samples - Heparin Lock Flush Solution may also be used after withdrawal of blood for laboratory tests. When heparin (or sodium chloride) would interfere with or alter the results of blood tests, the heparin solution should be cleared from the device by aspirating and discarding it before withdrawing the blood sample.

STORAGE

Store at room temperature below 25°C.

SUPPLIED

In vials of 10 ml containing:
Heparin Sodium 100 International units/ml
License No.: 1046928762

In vials of 10 ml containing:
Heparin Sodium 10 International units/ml
License No.: 1140529577

Manufacturer: Kamada Ltd., Beit Kama, Israel.
License Holder: Kamada Ltd., Beit Kama, Israel.

The format of this leaflet has been determined by the Ministry of Health and its content thereof was checked and approved by them in March 2012

KAMADA

3200000334-03