Baxter

Heparin Sodium and 0.9% Sodium Chloride Injection

in Plastic Container

Viaflex® Plus Container

APPROVED

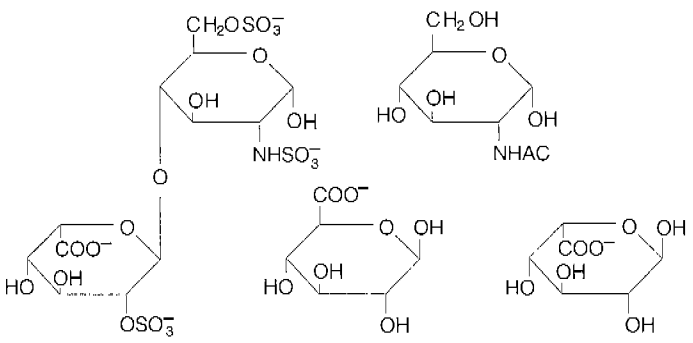
Labeling: SLR-033/035 AF
NDA No: 18-609 Re'd. 5-8-01
Reviewed by: Cherry 8/21/01

AUG 21 2001

Description

Heparin is a heterogenous 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 subunits):



(1) (2) (3) (4) (5)

...n Sodium and 0.9% Sodium Chloride Injection is a buffered, sterile, nonpyrogenic solution of ...parin Sodium, USP derived from porcine intestinal mucosa, standardized for anticoagulant activity supplied in single dose containers for vascular administration. It contains no antimicrobial agents. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram. Composition, osmolarity, pH and ionic concentration are shown in Table 1.

Table 1

	Size (mL)	Composition: Heparin Sodium, USP (units/mL)	Composition: Sodium Chloride, USP (NaCl) (g/L)	Composition: Dibasic Sodium Phosphate Heptahydrate, USP ($Na_2HPO_4 \cdot 7H_2O$) (g/L)	Composition: Citric Acid Hydrous, USP ($C_6H_8O_7 \cdot H_2O$) (g/L)	*Osmolality (mOsmol/L) (actual)	pH	Ionic Concentration (mEq/L): Sodium	Ionic Concentration (mEq/L): Chloride	Ionic Concentration (mEq/L): Phosphate (as $HPO_4^{=}$)	Ionic Concentration (mEq/L): Citrate
1000 USP Heparin Units and 0.9% Sodium Chloride Injection	500	2	9	4.34	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6
2000 USP Heparin Units and 0.9% Sodium Chloride Injection	1000	2	9	4.34	0.4	322	7.0 (6.0 to 8.0)	186	154	32 (16 mmol/L)	6

*Normal physiologic osmolarity range is approximately 280 to 310 mOsmol/L.
Administration of substantially hypertonic solutions (≥ 600 mOsmol/L) may cause vein damage.

This Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146® Plastic). Viaflex® Plus on the container indicates the presence of a drug additive in a drug vehicle. The Viaflex® Plus plastic container system utilizes the same container as the Viaflex® plastic container system. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

...cal Pharmacology

...n 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.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

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

Indications and Usage

Heparin Sodium and 0.9% Sodium Chloride Injection at a concentration of 2 units/mL is indicated as an aid in the maintenance of catheter patency.

Contraindications

Heparin sodium should not be used in 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 (see **Warnings**), except when this is due to disseminated intravascular coagulation.

Warnings

Hypersensitivity: Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

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.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular - Subacute bacterial endocarditis. Severe hypertension.

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

Hematologic - Conditions associated with increased bleeding tendencies, such as hemophilia, 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 hemorrhage occurs, heparin sodium should be discontinued promptly (see **Overdosage**).

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 (see White Clot Syndrome, **Precautions**), 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 ion should be used with great care in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there exists edema with sodium retention.

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

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

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

Precautions

1. **General**

   a. 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 possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

   b. Heparin Resistance:

   Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

   c. Increased Risk in Older Patients, Especially Women:

   A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

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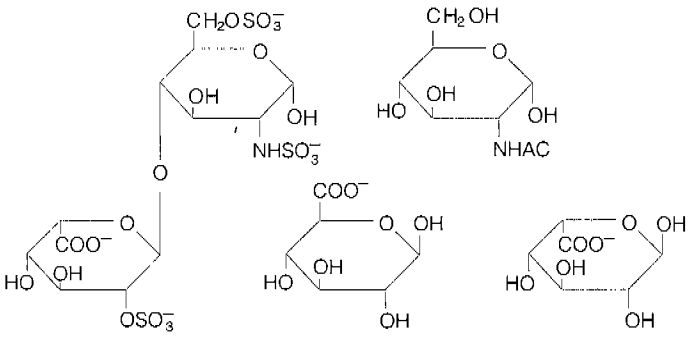

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