Intravenous Solutions with Heparin Sodium Injection

Rx only

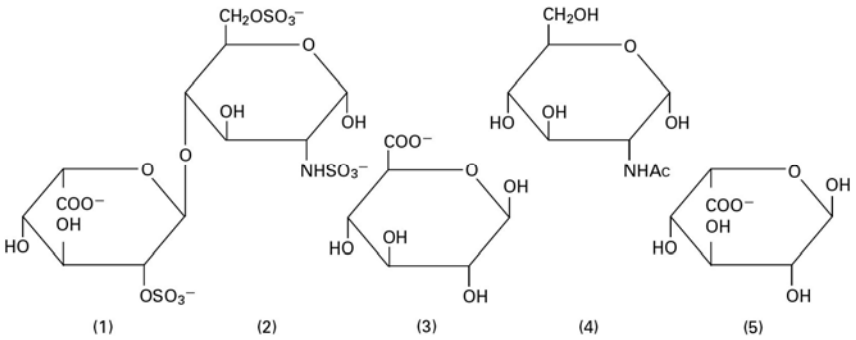
12,500 or 25,000 USP Units of Heparin Sodium in
0.45% Sodium Chloride Injection
Flexible Plastic Container

DESCRIPTION

Intravenous solutions with heparin sodium (derived from porcine intestinal mucosa) are sterile, nonpyrogenic fluids for intravenous administration. They contain no bacteriostat or antimicrobial agent or added buffer. Edetate disodium, anhydrous is added as a stabilizer. The solution may contain sodium hydroxide and/or hydrochloric acid for pH adjustment. See Table for summary of contents and characteristics of these solutions.

Heparin Sodium, USP 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. The potency is determined by a biological assay using a USP reference standard based on units of heparin activity per milligram.

Structure of Heparin Sodium (representative subunits):



Sodium Chloride, USP is chemically designated NaCl, a white crystalline compound freely soluble in water.

Water for Injection, USP is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated polyvinyl chloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

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 in 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.

Peak plasma levels of heparin are achieved 2 to 4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes. Liver and the reticuloendothelial system are the site of biotransformation. The biphasic elimination curve, a rapidly declining alpha phase (^{t}½ = 10') and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

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

Hypotonic concentrations of sodium chloride are suited for parenteral maintenance of water requirements when only small quantities of salt are desired.

Sodium chloride in water dissociates to provide sodium (Na^+) and chloride (Cl^-) ions. Sodium (Na^+) is the principal cation of the extracellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Chloride (Cl^-) has an integral role in buffering action when oxygen and carbon dioxide exchange occurs in the red blood cells. The distribution and excretion of sodium (Na^+) are largely under the control of the kidney which maintains a balance between intake and output.

Water is an essential constituent of all body tissues and accounts for approximately 70% of total body weight.

Average normal adult daily requirements range from two to three liters (1.0 to 1.5 liters each for insensible water loss by perspiration and urine production).

Water balance is maintained by various regulatory mechanisms. Water distribution depends primarily on the concentration of electrolytes in the body compartments and sodium (Na^+) plays a major role in maintaining physiologic equilibrium.

INDICATIONS AND USAGE

Heparin sodium is indicated for:

- Atrial fibrillation with embolization;
- Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);
- Prevention of clotting in arterial and heart surgery;
- Prophylaxis and treatment of peripheral arterial embolism;
- As an anticoagulant in extracorporeal circulation, and dialysis procedures.

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

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.

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 a 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 in patients receiving heparin has been reported at frequencies up to 30%. It can occur 2 to 20 days (average 5 to 9) following the onset of heparin therapy. Obtain platelet counts before and periodically during heparin therapy. Monitor thrombocytopenia of any degree closely. If the count falls below 100,000/mm^3 or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT and HITT, and, if necessary, administer an alternative anticoagulant (see ***Heparin-induced Thrombocytopenia and Heparin-Induced Thrombocytopenia and Thrombosis***).

Heparin-Induced Thrombocytopenia and Heparin-Induced Thrombocytopenia and Thrombosis: 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 known 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. Monitor thrombocytopenia of any degree

closely. If the platelet count falls below 100,000/mm^3 or if recurrent thrombosis develops, promptly discontinue heparin, evaluate for HIT and HITT, and, if necessary, administer an alternative anticoagulant.

HIT and HITT 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.

Solutions containing sodium ions should be used with great care, if at all, 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 these 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 administered parenteral solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of such solutions.

In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention.

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

As the dosage of solutions of heparin sodium must be titrated to individual patient response, additive medications should not be delivered via this solution.

PRECAUTIONS

General:

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

b. **Increased Risk to Older Patients, Especially Women:**
A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

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**).

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 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 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.

Drug/Laboratory Test Interactions:

Hyperaminotransferasemia: 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.

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.

Pregnancy:
Pregnancy Category C. There are no adequate and well-controlled studies on heparin use in pregnant women. In published reports, heparin exposure during pregnancy did not show evidence of an increased risk of adverse maternal or fetal outcomes in humans. Heparin sodium does not cross the placenta, based on human and animal studies. Administration of heparin to pregnant animals at doses higher than the maximum human daily dose based on body weight resulted in increased resorptions. Use heparin sodium during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a published study conducted in rats and rabbits, pregnant animals received heparin intravenously during organogenesis at a dose of 10,000 units/kg/day, approximately 10 times the maximum human daily dose based on body weight. The number of early resorptions increased in both species.

There was no evidence of teratogenic effects.

Nursing Mothers: Due to its large molecular weight, heparin is not likely to be excreted in human milk, and any heparin in milk would not be orally absorbed by a nursing infant. Exercise caution when administering Heparin Sodium to a nursing mother.

Pediatric Use: There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience (see **DOSAGE AND ADMINISTRATION**, ***Pediatric Use***).

Geriatric Use: A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (see **PRECAUTIONS**, ***General***). Clinical studies indicate that lower doses of heparin may be indicated in these patients (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS
Hemorrhage: Hemorrhage is the chief complication that may result from heparin therapy (see **WARNINGS**). 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 hemorrhagic complications may be difficult to detect:

a. Adrenal hemorrhage, 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 hemorrhage 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 the patient's death.

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

c. Retroperitoneal hemorrhage.

Local Irritation: Local irritation, erythema, mild pain, hematoma 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.

Hypersensitivity: Generalized 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 to 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.

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.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

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 (1% solution) 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 USP heparin units. 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.

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, the labeling of Protamine Sulfate Injection, USP products should be consulted.

In the event of overhydration or solute overload, re-evaluate the patient and institute appropriate corrective measures. See **WARNINGS** and **PRECAUTIONS**.

DOSAGE AND ADMINISTRATION

Heparin sodium is not effective by oral administration and these premixed formulations should be given by intermittent intravenous injection or intravenous infusion.

The dosage of heparin sodium should be adjusted according to the patient's coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection during the early stages of treatment and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times the normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value.

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.

Converting to Oral Anticoagulant: When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. If continuous IV heparin infusion is used, prothrombin time can usually be measured at any time.

In converting from heparin to an oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

Therapeutic Anticoagulant Effect with Full-Dose Heparin

Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage schedules may be used as guidelines:

Method of Administration	Frequency	Recommended Dose*
Intermittent Intravenous Injection	Initial Dose	10,000 Units, either undiluted or in 50 – 100 mL of 0.45% Sodium Chloride Injection, USP
	Every 4 to 6 hours	5,000 – 10,000 Units, either undiluted or in 50 – 100 mL of 0.45% Sodium Chloride Injection, USP
Continuous Intravenous Infusion	Initial Dose	5,000 Units by IV injection
	Continuous	20,000 – 40,000 Units/24 hours in 0.45% Sodium Chloride Injection, USP

*Based on 150 lb. (68 kg) patient.

Pediatric Use: There are no adequate and well controlled studies on heparin use in pediatric patients. Pediatric dosing recommendations are based on clinical experience. In general, the following dosage schedule may be used as a guideline in pediatric patients:

Initial Dose 75 to 100 units/kg (IV bolus over 10 minutes)

Maintenance Dose Infants: 25 to 30 units/kg/hour;

Infants < 2 months have the highest requirements (average 28 units/kg/hour)

Children > 1 year of age: 18 to 20 units/kg/hour;

Older children may require less heparin, similar to weight-adjusted adult dosage

Monitoring Adjust heparin to maintain aPTT of 60 to 85 seconds, assuming this reflects an anti-Factor Xa level of 0.35 to 0.70.

Geriatric Use: Patients over 60 years of age may require lower doses of heparin.

Surgery of the Heart and Blood Vessels: Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight. Frequently, a dose of 300 units per kilogram is used for procedures estimated to last less than 60 minutes or 400 units per kilogram for those estimated to last longer than 60 minutes.

Extracorporeal Dialysis: Follow equipment manufacturer's operating directions carefully.

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. (See **PRECAUTIONS**.)

Do not administer unless the solution is clear and seal is intact. Discard unused portion.

INSTRUCTIONS FOR USE

To Open

Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Preparation for Administration
(Use aseptic technique)

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated.
   NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber.
6. Open flow control clamp and clear air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Regulate rate of administration with flow control clamp.

WARNING: DO NOT USE FLEXIBLE CONTAINER IN SERIES CONNECTIONS.

HOW SUPPLIED

Intravenous solutions with heparin sodium are supplied in single-dose flexible plastic containers in varied sizes and concentrations as shown in the accompanying Table.

Content and Characteristics

		Per 100 mL			Per 1000 mL						
NDC No.	Product	Heparin Sodium (Units/ mL)	Heparin Sodium (Units)	Sodium Chloride (grams)	Edetate Disodium (anhydrous) (mg)	Sodium Na^+	Chloride Cl^-	Tonicity	Osmolarity mOsmol/L (calc.)	pH (range)	Solution Volume
0409-7650-62	Heparin Sodium 25,000 USP Units in 0.45% Sodium Chloride Injection	100	10,000	0.45	10	77 mEq	77 mEq	Hypotonic	155	6.1 (5.0 - 7.5)	250 mL
0409-7651-62	Heparin Sodium 12,500 USP Units in 0.45% Sodium Chloride Injection	50	5,000	0.45	10	77 mEq	77 mEq	Hypotonic	155	6.1 (5.0 - 7.5)	250 mL
0409-7651-03	Heparin Sodium 25,000 USP Units in 0.45% Sodium Chloride Injection	50	5,000	0.45	10	77 mEq	77 mEq	Hypotonic	155	6.1 (5.0 - 7.5)	500 mL

Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing.

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