PRESCRIBING INFORMATION

PROTAMINE SULFATE INJECTION USP

10 mg/mL

Heparin Antagonist

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PHARMACEUTICAL INFORMATION

Protamines are simple proteins of low molecular weight that are rich in arginine and strongly basic. They occur in the sperm of salmon and certain other species of fish.

Protamine sulfate occurs as a fine white or off-white amorphous or crystalline powder. It is sparingly soluble in water. The pH is between 6 and 7. The cationic hydrogenated protamine at a pH of 6.8 to 7.1 reacts with anionic heparin at a pH of 5.0 to 7.5 to form an inactive complex.

Protamine Sulfate Injection USP is a sterile, isotonic solution of protamine sulfate. It acts as a heparin antagonist. It is also a weak anticoagulant.

Protamine Sulfate Injection USP is administered intravenously.

ACTION AND CLINICAL PHARMACOLOGY

When administered alone, protamine has an anticoagulant effect. However, when it is given in the presence of heparin (which is strongly acidic), a stable salt is formed and the anticoagulant activity of both drugs is lost.

Protamine sulfate has a rapid onset of action. Neutralization of heparin occurs within 5 minutes after intravenous administration of an appropriate dose of protamine sulfate. Although the metabolic fate of the heparin-protamine complex has not been elucidated, it has been postulated that protamine sulfate in the heparin-protamine complex may be partially metabolized or may be attacked by fibrinolysin, thus freeing heparin.

INDICATIONS AND CLINICAL USE

Protamine Sulfate Injection USP is indicated in the treatment of heparin overdosage.

CONTRAINDICATIONS

Protamine sulfate is contraindicated in patients who have shown previous intolerance to the drug.

WARNINGS

Hyperheparinemia or bleeding has been reported in experimental animals and in some patients 30 minutes to 18 hours after cardiac surgery (under cardiopulmonary bypass) in spite of complete neutralization of heparin by adequate doses of protamine sulfate at the end of the operation. Therefore, it is important to keep the patient under close observation after cardiac surgery. Additional doses of protamine sulfate should be administered if indicated by coagulation studies, such as the heparin titration test with protamine and the determination of plasma thrombin time.

Too rapid administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions (see DOSAGE AND ADMINISTRATION). Facilities to treat shock should be available.

PRECAUTIONS

General

Because of the anticoagulant effect of protamine, it is unwise to give more than 50 mg over a short period unless a larger dose is clearly needed.

Patients with a history of allergy to fish may develop hypersensitivity reactions to protamine, although to date no relationship has been established between allergic reactions to protamine and fish allergy.

Previous exposure to protamine through use of protamine-containing insulins or during heparin neutralization may predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug. Reports of the presence of antiprotamine antibodies in the sera of infertile or vasectomized men suggest that some of these individuals may react to use of protamine sulfate.

Fatal anaphylaxis has been reported in one patient with no prior history of allergies.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies have not been performed to determine potential for carcinogenicity, mutagenicity, or impairment of fertility.

Special Populations

Pregnant Women: Animal reproduction studies have not been conducted with protamine sulfate. It is also not known whether protamine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Protamine sulfate should be given to a pregnant woman only if clearly needed.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when protamine sulfate is administered to a nursing woman.

Pediatrics: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The intravenous administration of protamine sulfate may cause a sudden fall in blood pressure and bradycardia. Other reactions include transitory flushing and feeling of warmth, dyspnea, nausea, vomiting, and lassitude. Back pain has been reported in conscious patients undergoing such procedures as cardiac catheterization.

Severe adverse reactions have been reported including:

- Anaphylaxis that resulted in severe repiratory distress, circulatory collapse, and capillary leak (see PRECAUTIONS). Fatal anaphylaxis has been reported in one patient with no prior history of allergies.
- Anaphylactoid reactions with circulatory collapse, capillary leak, and noncardiogenic pulmonary edema, acute pulmonary hypertension.

Complement activation by the heparin-protamine complexes, release of lysosomal enzymes from neutrophils, and prostaglandin and thromboxane generation have been associated with the development of anaphylactoid reactions.

Severe and potentially irreversible circulatory collapse associated with myocardial failure and reduced cardiac output can also occur. The mechanism(s) of this reaction and the role played by concurrent factors are unclear.

High-protein, noncardiogenic pulmonary edema associated with the use of protamine has been reported in patients on cardiopulmonary bypass who are undergoing cardiovascular surgery. The etiologic role of protamine in the pathogenesis of this condition is uncertain, and multiple factors have been present in most cases. The condition has been reported in association with administration of certain blood products, other drugs, cardiopulmonary bypass alone, and other etiologic factors. It is difficult to treat, and it can be life-threatening. Because fatal anaphylactic and anaphylactoid reactions have been reported after the administration of protamine sulfate, the drug should be given only when resuscitation techniques and treatment of anaphylactic and anaphylactoid shock are readily available.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

DRUG INTERACTIONS

Protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins (see DOSAGE AND ADMINISTRATION).

OVERDOSAGE

Signs and Symptoms: Overdose of protamine sulfate may cause bleeding. Protamine has a weak anticoagulant effect due to an interaction with platelets and with many proteins including fibrinogen. This effect should be distinguished from the rebound anticoagulation that may occur 30 minutes to 18 hours following the reversal of heparin with protamine.

Rapid administration of protamine is more likely to result in bradycardia, dyspnea, a sensation of warmth, flushing, and severe hypotension. Hypertension has also occurred.

The median lethal intravenous dose (LD_{50}) of protamine sulfate is 50 mg/kg in mice. Serum concentrations of protamine sulfate are not clinically useful. Information is not available on the amount of drug in a single dose that is associated with overdosage or is likely to be life-threatening.

Replace blood loss with blood transfusions or fresh frozen plasma. If the patient is hypotensive, consider fluids, epinephrine, dobutamine, or dopamine.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Each mg of protamine sulfate neutralizes approximately 90 USP units of heparin activity derived from lung tissue or about 115 USP units of heparin activity derived from intestinal mucosa.

Protamine Sulfate Injection USP should be given by very slow intravenous injection in doses not to exceed 50 mg of protamine sulfate in any 10-minute period (see WARNINGS).

Protamine Sulfate Injection USP is intended for injection without further dilution; however, if further dilution is desired, Dextrose Injection 5% or Sodium Chloride Injection 0.9% may be used. Diluted solutions should not be stored since they contain no preservative.

Protamine sulfate should not be mixed with other drugs without knowledge of their compatibility, because protamine sulfate has been shown to be incompatible with certain antibiotics, including several of the cephalosporins and penicillins.

Because heparin disappears rapidly from the circulation, the dose of protamine sulfate required also decreases rapidly with the time elapsed following intravenous injection of heparin. For example, if the protamine sulfate is administered 30 minutes after the heparin, one half of the usual dose may be sufficient.

The dosage of protamine sulfate sould be guided by blood coagulation studies (see WARNINGS).

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Protamine Sulfate Injection USP is a sterile, isotonic, preservative free solution of protamine sulfate.

Each mL contains: protamine sulfate 10 mg, sodium chloride 9 mg, sulfuric acid and/or dibasic sodium phosphate to adjust pH and water for injection.

Protamine Sulfate Injection USP, 10 mg/mL, is available in single use vials of 5 mL, boxes of 10, and of 25 mL, boxes of 1.

The chlorobutyl rubber stopper is not made with natural rubber latex.

STORAGE AND STABILITY

Discard unused portion.
Store between 15 and 30°C.
Do not freeze.