PROTAMINE

Introduction

INN: Protamine sulfate 9

BAN: Protamine sulphate 9

Category

Antidote (to heparin).

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Toxicity, heparin (treatment) or

[Toxicity, enoxaparin (treatment)] *¾Protamine is indicated in the treatment of severe heparin overdose resulting in hemorrhage 3, 4, 8, 12.

It is indicated to neutralize heparin that is administered during extracorporeal circulation in arterial and cardiac surgery or dialysis procedures 7 ; also, it may be used to neutralize the hemorrhagic effects following overdose of the low molecular weight heparin, enoxaparin 5, 6, 7.

Transfusion of whole blood or fresh frozen plasma may also be required to replace lost volume 10, 12 if hemorrhaging has been severe; this may dilute, but will not neutralize, the effects of heparin.

Unaccepted

Protamine is not used in treating minor heparin overdose that may respond to withdrawal of heparin, or in treating hemorrhage not caused by heparin.

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Source¾Obtained from the sperm of salmon and certain other species of fish.Chemical group¾Protamines are strongly basic low molecular weight proteins, containing large amounts of arginine.

pH¾6 to 7.

Sparingly soluble in water.

Mechanism of action/Effect:

Protamine is a strongly basic substance that combines with the strongly acidic heparin to form a stable (salt) 12 complex 3, 4, 8.

The protamine-heparin complex has no anticoagulant activity 12.

Heparin produces its effects indirectly, apparently by forming a complex with and producing a conformational change in the antithrombin III (heparin cofactor) molecule, resulting in potentiation of antithrombin III activity. One study has indicated that by combining with heparin, protamine causes a dissociation of the heparin-antithrombin III complex, resulting in loss of its anticoagulant activity.

Other actions/effects:

Protamine is a weak anticoagulant when administered in the absence of heparin or in doses larger than those required to neutralize heparin 10 , but it is not used as an anticoagulant 3, 4, 8, 12.

This anticoagulant effect may be caused by protamine's antithromboplastin activity, which results in the inhibition of thrombin generation.

Onset of action:

Within 5 minutes 8, 12.

Duration of action:

2 hours; dependent on body temperature.

Precautions to Consider

Carcinogenicity/Tumorigenicity/Mutagenicity

Studies have not been done to determine the potential of protamine for carcinogenicity/tumorigenicity/mutagenicity 12.

Pregnancy/Reproduction

Fertility¾Studies have not been done to determine the potential of protamine for impairment of fertility 12.

Pregnancy¾Studies have not been done in humans.

Studies have not been done in animals. 1, 3, 4, 8, 12

FDA Pregnancy Category C 1, 3, 4, 12.

Breast-feeding

It is not known whether protamine is distributed into breast milk 2, 3, 4, 12.

However, problems in humans have not been documented.

Pediatrics

Appropriate studies on the relationship of age to the effects of protamine have not been performed in the pediatric population. Safety and efficacy have not been established 12.

Geriatrics

Appropriate studies on the relationship of age to the effects of protamine have not been performed in the geriatric population. However, geriatrics-specific problems that would limit the usefulness of this medication in the elderly are not expected.

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist

>> Allergic reaction to protamine, history of 3, 4, 8, 12 or

Allergy to fish 12 or

Antibodies to human protamine, which may occur in the sera of infertile or vasectomized men 3, 4, 12 or

Prior exposure to protamine or other protamine-containing medications, e.g., protamine insulin 3, 4, 12

(increased risk of allergic reaction)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Blood coagulation tests

(recommended as a guide to protamine efficacy and dosage; in the operating room, activated clotting time [ACT], either manual or automated, is most often used to monitor neutralization of large doses of heparin)

Blood titration tests with protamine

(may be necessary as a guide to protamine dosage, especially when large doses of heparin have been administered)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent¾usually caused by too-rapid administration of medicationBradycardia 1, 2, 3, 4, 8, 12; cardiovascular collapse or shock¾may be caused by a direct myocardial effect and/or peripheral vasodilatation 1, 2, 3, 4; decrease in blood pressure, sudden¾may reach hypotensive levels 1, 2, 3, 4, 8, 12; dyspnea 1, 2, 3, 4, 8, 12

Incidence less frequent

Anaphylactic or anaphylactoid reaction 1, 2, 3, 4, 8, 12; bleeding¾may be caused by protamine overdose or by a rebound of heparin activity 2, 3, 4, 12; hypertension, pulmonary and/or systemic 1, 2, 3, 4, 8, 12; noncardiogenic pulmonary edema¾reported in patients on cardiopulmonary bypass undergoing cardiovascular surgery 2, 3, 4, 8, 12

Note: Anaphylactic or anaphylactoid reactions may be more likely to occur in patients with a history of allergy to fish (because protamine is prepared from the sperm or mature testes of fish [salmon or related species]); however, a definite relationship between allergy to fish and allergic reactions to protamine sulfate has not been established 12.

Patients who previously have been exposed to protamine through the use of protamine-containing insulin, and patients with protamine antibodies developed from prior heparin neutralization, may experience life-threatening reactions or fatal anaphylaxis upon receiving large doses of intravenous protamine 12.

Male patients who are infertile or have had a vasectomy may develop antiprotamine antibodies to human protamine, which may predispose these patients to allergic reactions to protamine derived from nonhuman sources 12.

In addition, fatal anaphylaxis has been reported in one patient with no prior history of allergies 12.

The development of anaphylactoid reactions (reactions similar to anaphylaxis) may occur when protamine is administered too rapidly 1, 2, 3, 4, 8, 12.

Anaphylactoid reactions have been associated with compliment activation by heparin-protamine complexes, release of lysosomal enzymes from neutrophils, and prostaglandin and thromboxane generation 12.

Those indicating need for medical attention only if they continue or are bothersome

Incidence less frequent or rare

Back pain¾reported rarely in conscious patients undergoing procedures such as cardiac catheterization 2, 3, 4, 8, 12; feeling of warmth; feeling of weakness; flushing; nausea or vomiting 3, 4, 8, 12

Overdose

For specific information on the agents used in the management of protamine overdose, see the Sympathomimetic Agents¾Cardiovascular Use (Parenteral-Systemic) monograph.

For more information on the management of overdose, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Early signs of excessive anticoagulation

Bleeding from gums when brushing teeth; heavy bleeding or oozing from cuts or wounds; unexplained bruising or purplish areas on skin; unexplained nosebleeds; unusually heavy or unexpected menstrual bleeding

Signs and symptoms of internal bleeding

Abdominal pain or swelling; back pain or backaches; blood in urine; bloody or black, tarry stools; constipation caused by hemorrhage-induced paralytic ileus or intestinal obstruction; coughing up blood; dizziness; headaches; severe or continuing joint pain, stiffness, or swelling; vomiting of blood or material that looks like coffee grounds

Treatment of overdose

In the event of bleeding due to protamine overdose, protamine should be discontinued. If bleeding is caused by a rebound effect of heparin, additional protamine administration may be necessary, as indicated by the appropriate blood coagulation test results. The heparin titration test with protamine, and the determination of plasma thrombin time, are commonly used in this setting. 12

For severe hemorrhaging, transfusion of whole blood or fresh frozen plasma also may be required. Hypotensive patients may require additional intravenous fluids, epinephrine, dobutamine, or dopamine. 12

General Dosing Information

Protamine sulfate is administered by very slow intravenous injection 3, 4, 5, 6, 8, 12.

A concentration of 10 mg of protamine sulfate per mL is usually used.

Facilities for treating shock and other symptoms of anaphylaxis should be available whenever protamine sulfate is administered 3, 4, 5, 8, 12.

Prior to administration of protamine, it is recommended that care be taken to assure that the patient's blood volume is adequate. Hypovolemia may increase the risk of peripheral vasodilatation,

which may lead to cardiovascular collapse, especially following too-rapid administration of protamine.

The stated doses are intended as guidelines only. It is strongly recommended that blood coagulation tests be used to determine the optimum dosage of protamine [3, 4, 8], especially when neutralizing large doses of heparin given during cardiac or arterial surgery.

Tests used to monitor protamine therapy include activated clotting time (ACT), activated partial thromboplastin time (APTT), thrombin time (TT), and/or direct titration of a sample of the patient's blood with protamine. The tests should be performed at least 5 to 15 minutes following initial administration of protamine and repeated as necessary. Neutralization of heparin used during extracorporeal circulation may be monitored using sequential ACT testing with a dose-response curve that correlates the test results with the quantity of heparin remaining to be neutralized. However, hypothermia may decrease the accuracy of these tests. APTT and TT may not be useful in monitoring protamine therapy after administration of enoxaparin because enoxaparin, in therapeutic doses, does not alter the value of these tests [5, 6, 11].

Bleeding may recur if too much protamine, which has anticoagulant activity of its own, is administered or if the effects of heparin persist longer than the effects of protamine. The half-life of heparin is 60 to 360 minutes, with an average of 90 minutes. The half-life is dose-dependent (the larger the dose, the longer the half-life) and subject to intrapatient and interpatient variation. It has been proposed that the rebound of heparin effect may be caused by metabolism of protamine with resultant dissociation of the heparin-protamine complex and/or by release of heparin from storage or binding sites. Heparin rebound is especially likely to occur following administration of large doses of heparin, such as those used during cardiopulmonary bypass procedures, and has been reported to occur as late as 18 hours following initial complete neutralization of heparin. Prolonged monitoring of the patient is necessary so that additional doses of protamine may be administered, as determined by blood coagulation test results. [3, 4, 8]

As time elapses following intravenous administration of heparin, less protamine is required because of rapidly decreasing serum heparin concentrations. For example, 30 minutes after the intravenous administration of heparin, approximately one-half the amount of protamine sulfate is sufficient for neutralization. [3, 4, 8] However, absorption of heparin may be prolonged following subcutaneous administration. For neutralizing heparin given subcutaneously, an initial loading dose of 25 to 50 mg of protamine sulfate, followed by administration of the remainder of the calculated protamine sulfate dose as an intravenous infusion over a period of 8 to 16 hours, has been recommended.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PROTAMINE SULFATE INJECTION USP

Usual adult and adolescent dose

Heparin toxicity¾

Intravenous, 1 mg of protamine sulfate for approximately every 100 USP units of heparin to be neutralized [4], or as determined by blood coagulation test results [3, 4].

(One mg of protamine sulfate neutralizes approximately 90 USP units of heparin activity derived from beef lung tissue or approximately 115 USP units of heparin activity derived from porcine intestinal mucosa [8, 12].)

[Enoxaparin toxicity] *¾

Intravenous, 1 mg of protamine sulfate for approximately every 1 mg of enoxaparin to be neutralized [5, 6].

Note: Protamine sulfate injection should be administered at a rate of 5 mg per minute, not to exceed 50 mg [3, 4, 12] in any ten-minute period [8].

Additional doses may be required as indicated by blood coagulation studies.

Since protamine has anticoagulant activity of its own, it is not advisable to administer more than 100 mg of protamine sulfate over a two-hour period of time (the duration of action of protamine), unless blood coagulation tests indicate a larger requirement.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾10 mg per mL (Rx) [Generic] 12

Canada¾10 mg per mL (Rx) [Generic] 8

Packaging and storage:

Store under refrigeration between 2 and 8 °C (36 and 46 °F) [3, 8, 12].

Protect from freezing.

Preparation of dosage form:

Protamine sulfate injection is intended for use without further dilution; however, if further dilution is desired, 5% dextrose injection or 0.9% sodium chloride injection may be used [3, 4, 8, 12].

Stability:

Contains no preservatives; discard unused portion of opened container. Diluted solutions should not be stored because they contain no preservative. [3, 4, 8, 12]

Incompatibilities:

Protamine sulfate solutions are incompatible with certain antibiotics, including several of the cephalosporins and penicillins. It is recommended that no other medications be mixed with protamine sulfate unless they are known to be compatible. [3, 4, 8, 12]

PROTAMINE SULFATE FOR INJECTION USP

Usual adult and adolescent dose

See Protamine Sulfate Injection USP .

Usual pediatric dose

Safety and efficacy have not been established.

Size(s) usually available:

U.S.¾Not commercially available.

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Stability:

Reconstituted solutions should be refrigerated and used within 24 hours.

Incompatibilities:

Protamine sulfate solutions are incompatible with certain antibiotics, including several of the cephalosporins and penicillins. It is recommended that no other medications be mixed with protamine sulfate unless they are known to be compatible.