Protamine

Newborn use only

2021

<table>
<tr><td>Alert</td><td>Stopping unfractionated heparin (UFH) infusion is adequate in most instances including overdose if no bleeding.
Reversal of low molecular weight heparin (e.g. enoxaparin) by protamine is incomplete.
Rapid IV injection of protamine can cause anaphylactic reaction and cardiovascular collapse. Facilities for resuscitation and treatment of shock should be available.
Protamine acts as an anticoagulant at very high doses.
Protamine has variable dose-response and a narrow therapeutic window.</td></tr>
<tr><td>Indication</td><td>Reverses anticoagulant effects of unfractionated and low molecular weight heparin.</td></tr>
<tr><td>Action</td><td>Protamine forms a neutral 1:1 complex and strips heparin from antithrombin III. (1) It inhibits the inactivation of thrombin, factor XII and thrombin-fibrinogen interaction. It reduces prothrombin activator, prolongs prothrombin time, shortens thrombin time, and selectively precipitates fibrinogen. (2, 3)</td></tr>
<tr><td>Drug type</td><td>Antidote to heparin</td></tr>
<tr><td>Trade name</td><td>Protamine sulfate injection BP</td></tr>
<tr><td>Presentation</td><td>Ampoule contains 50 mg/5 mL of protamine sulfate</td></tr>
<tr><td>Dose</td><td>1. Protamine sulfate dose for UFH reversal (4)
<table><tr><th>Time Since Last Heparin Dose</th><th>Protamine dose per 100 units of heparin received in the last 2 hours</th></tr><tr><td><30 min</td><td>1 mg</td></tr><tr><td>30-60 min</td><td>0.5-0.75 mg</td></tr><tr><td>60-120 min</td><td>0.375-0.5 mg</td></tr><tr><td>>120 min</td><td>0.25-0.375 mg</td></tr></table>2. Protamine sulfate dose for reversal of enoxaparin or low molecular weight heparin (LMWH)
If within 3 to 4 hr of the administration of LMWH, dose of protamine is 1 mg per 1 mg of enoxaparin given. (5)</td></tr>
<tr><td>Dose adjustment</td><td>Therapeutic hypothermia – No information.
ECMO – Refer to local ECMO protocol.
Renal impairment – No information.
Hepatic impairment – No information.</td></tr>
<tr><td>Maximum dose</td><td>50 mg at any one time (except for reversal of UFH following cardiopulmonary bypass) (4)</td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV</td></tr>
<tr><td>Preparation</td><td>Usually not required.
May be diluted if necessary with sodium chloride 0.9% (6)</td></tr>
<tr><td>Administration</td><td>Slow infusion over 10 minutes (7)</td></tr>
<tr><td>Monitoring</td><td>Blood pressure (for hypotension) and heart rate (bradycardia) (8)
Bleeding
Monitor activated partial thromboplastin time (APTT) or other appropriate blood clotting parameters</td></tr>
<tr><td>Contraindications</td><td>Hypersensitivity to protamine or to any excipients.</td></tr>
<tr><td>Precautions</td><td>Patients with known hypersensitivity reactions to protamine-containing insulin or previous protamine therapy may be at risk of hypersensitivity reactions
Known hypersensitivity reactions to fish (8)</td></tr>
<tr><td>Drug interactions</td><td>None known (6, 8)</td></tr>
<tr><td>Adverse reactions</td><td>Hypotension, bradycardia, pulmonary hypertension, non-cardiogenic pulmonary oedema, transient flushing, anaphylaxis. (7, 8)</td></tr>
<tr><td>Compatibility</td><td>Fluids: Glucose 5%2 , Plasma-Lyte 148 via Y-site , sodium chloride 0.9%
Y-site: Some information is available. Consult the pharmacist, pharmacy department or medicines information service for advice.</td></tr>
<tr><td>Incompatibility</td><td>Fluids: No information.</td></tr>
</table>

	Drugs: Ampicillin, benzylpenicillin, cefazolin, cefotaxime, cefoxitin, ceftazidime, ceftriaxone, dexamethasone, folic acid, furosemide, heparin sodium, hydrocortisone sodium succinate, indometacin, insulin (Actrapid), ketorolac, methylprednisolone sodium succinate, pentamidine, phenobarbital, sugammadex (7)
Stability	Diluted solutions should be used immediately and should not be stored as it contains no preservatives.
Storage	Store below 25°C. (8)
Excipients	Sodium chloride, hydrochloric acid, sodium hydroxide, water for injections. (8)
Special comments	The rapid disappearance of protamine from the circulation could contribute to “heparin rebound" after initial adequate reversal of heparin. Repeated doses may be required to neutralise
Evidence	**Efficacy** When titrated with heparinised plasma, protamine neutralises its anticoagulant activity and restores thrombin generation. (3, 9, 10) This pharmacological action is used for reversing the anticoagulant effect of unfractionated heparin and low molecular weight heparin following accidental overdose or procedures requiring anticoagulation of in vitro blood-circuits. In neonates and children anticoagulation reversal with heparin, when used with individualised heparin dosage significantly reduces activation of coagulation cascade, fibrinolysis, blood loss, need for transfusion, ventilatory support and hospital stay after cardiac surgery with cardiopulmonary bypass. (11, 12) Equimolar concentrations of protamine sulfate neutralize anti-IIa activity of LMWH but result in only partial neutralization of its anti-Xa activity. (13) The dose of protamine sulfate required depends on the dose and type of LMWH used. Repeat doses of protamine may be required after subcutaneous LMWH. (14) **Safety** In neonates, protamine has been used for reversal of heparin effect following cardiac surgery requiring cardiopulmonary bypass and accidental heparin overdose. (9, 15) Hypersensitivity reactions to protamine sulfate may occur in patients with known hypersensitivity reactions to fish or those previously exposed to protamine therapy or protamine-containing insulin. (5) Some studies recommend use of peripheral venous catheter for administration as protamine delivery through a central line can cause an increase in plasma histamine levels and a decrease in systemic vascular resistance. (16) **Pharmacokinetics** In vitro studies suggest a significant effect at protamine plasma concentrations of 0.02 to 0.5 mg/mL. Protamine sulfate and the heparin/protamine complex are partially metabolized by fibrinolysin and free protamine is broken down by plasma protaminase. Half-life of protamine is reported to be 7.4 min, after a single intravenous dose of 0.5 mg/kg via infusion pump over 10 min in healthy volunteers. (17)
Practice points	• It is presumed that 1 mg of protamine neutralises anticoagulant effects of 1 mg (100 units) of heparin. • Half-life of heparin is short, so dose of protamine depends on time since the last heparin injection. • Obtain blood for PT and APTT 15 min after the administration of protamine sulphate. • Effects of LMWH can persist for up to 24 hours after administration, so repeat doses of protamine may be required. • Prolonged infusion of protamine is necessary if heparin was administered subcutaneously.
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