

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Poisonings**

MEDICINE MOTIVATION:

1. Executive Summary

Date: July 2018
Medicine (INN): Protamine
Medicine (ATC): V03AB14
Indication (ICD10 code): Anticoagulant poisoning [R58/T45.5 + (SDX: X44.99/ X64.99/ Y14.99)]
Antidote: Heparin over-dosage, following inadvertent excess intravenous
 Unlabelled use: Treatment of low molecular weight heparin (LMWH) overdose
Patient population: Adult
Prevalence of condition: unclear
Level of Care: Hospital level/ secondary level of care
Prescriber Level: Medical officer
Current standard of Care: n/a
Efficacy estimates: (preferably NNT) n/a
Motivator/reviewer name(s): Dr H Dawood
PTC affiliation: Greys hospital PTC

2. Name of author(s)/motivator(s): Dr H Dawood

3. Author affiliation and conflict of interest details

Affiliation: Greys hospital and Caprisa, UKZN; Chair of the Adult Hospital Level Committee (2017-2020)
Conflict of interests: Pfizer- SA Pneumococcal summit attendance; MSD: SAASP - Attendance of meetings; MSD: ECMID - Conference attendance; ACTA study- DSMB member; Adcock Ingram & Novartis - Speaker fees; IDSSA – President elect; HpCA – Ethics Committee member.

4. Introduction/ Background

An agent is needed for quick reversal of the action of heparin in case of bleeding after inadvertent administration of excess heparin or LMWH.

Protamine is a polypeptide which binds to unfractionated heparin and neutralizes its effect. Protamine is used to reverse the anticoagulant effects of heparin, especially after open heart surgery. It is also the treatment of choice in case of significant bleeding with heparin therapy.

Protamine is a highly alkaline protein molecule with a large positive charge and is a weak anticoagulant. When protamine is administered in the presence of heparin (strongly acidic and negatively charged), a stable salt is formed and the anticoagulant activity of both drugs is neutralisedⁱ. In the presence of LMWH, protamine incompletely reverses the antifactor Xa activity of LMWH^{ii, iii}.

Definitive evidence-based guidelines on dosing of protamine and frequency of monitoring are lacking. The American College of Chest Physicians recommends 1 mg of protamine per 100 anti-Xa units of LMWH in the first 8 hours, followed by 0.5 mg per 100 anti-Xa units if the bleeding continues^{iv}.

In the largest retrospective case series, van Veen and others described a cohort of 17 patients receiving the LMWH enoxaparin, in whom reversal was needed because of bleeding or surgery. Protamine use was associated with a reduction in bleeding; however, 3 of the patients continued to experience bleeding or re-bleeding, despite administration of protamine. Protamine had minimal effect on reducing anti-Xa levels in these patients^v

Protamine sulphate can cause severe hypotension, cardiovascular collapse, non-cardiogenic pulmonary oedema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension.

Risk factors include high dose or overdose, rapid administration, repeated doses, previous administration of protamine, and current or previous use of protamine-containing drugs (NPH insulin, protamine zinc insulin, and certain beta-blockers).

Allergy to fish, previous vasectomy, and severe left ventricular dysfunction and abnormal preoperative pulmonary hemodynamics also may be risk factors. In patients with any of these risk factors, the risk to benefit of administration of protamine should be carefully considered.

Vasopressors and resuscitation equipment should be immediately available in case of a severe reaction to protamine. Protamine should not be given when bleeding occurs without prior heparin therapy.

Protamine has an onset of action following IV administration of approximately 5 minutes and a half-life of about 7 minutes^{vi}.

Neutralisation dose of protamine for IV Heparin Over-dose^{vii} (Caravati 2004)

Time Elapsed	Dose of Protamine (mg) to Neutralize 100 units of Heparin
Immediate	1 to 1.5
30 to 60 min	0.5 to 0.75
>2 h	0.25 to 0.375

5. Purpose/Objective

-P: *adults*

-I: *protamine sulphate*

-C: *none*

-O: *prevent life-threatening bleeding after inadvertent administration of excess heparin or LMWH*

PICO: Is protamine a suitable antidote for heparin overdose in adult patients?

6. Methods:

a. **Data sources:** Medline, PubMed and UptoDate®

b. **Search strategy :** “protamine sulphate”

c. **Excluded studies:** No systematic reviews of RCTs or RCTs could be retrieved from the published literature.

d. **Evidence synthesis and quality:** Available evidence that could be found were case reports and case series evidence for use inadvertent IV administration of heparin.

7. Alternative agents: nil

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS				
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p> Confident Not confident Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>	Lack of randomised controlled trials, available data includes case reports and case series.				
BENEFITS & HARMS	<p>Do the desirable effects outweigh the undesirable effects?</p> <p> Benefits outweigh harms Harms outweigh benefits Benefits = harms or uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>					
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p> Yes No <input type="checkbox"/> <input checked="" type="checkbox"/> </p> <p>List the members of the group: n/a</p> <p>List specific exclusion from the group: n/a</p>	<p>Rationale for therapeutic alternatives included: n/a</p> <p>References: n/a</p> <p>Rationale for exclusion from the group: n/a</p> <p>References: n/a</p>				
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p> Minor Major Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p> <p>Is the option acceptable to key stakeholders?</p> <p> Yes No Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>					
RESOURCE USE	<p>How large are the resource requirements?</p> <p> More intensive Less intensive Uncertain <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> </p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th><th>Cost (ZAR)</th></tr> </thead> <tbody> <tr> <td>Protamine sulphate 50mg/5ml inj</td><td>60.07*</td></tr> </tbody> </table> <p>*Contract circular HP06-2017SVP</p> <p>Additional resources: n/a</p>	Medicine	Cost (ZAR)	Protamine sulphate 50mg/5ml inj	60.07*
Medicine	Cost (ZAR)					
Protamine sulphate 50mg/5ml inj	60.07*					
EQUITY	<p>Would there be an impact on health inequity?</p> <p> Yes No Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>					
FEASIBILITY	<p>Is the implementation of this recommendation feasible?</p> <p> Yes No Uncertain <input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/> </p>					

Type of recommendation	We recommend against the option	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Recommendation: Based on this evidence review, the Adult Hospital Level Committee was of the opinion that protamine not be recommended for inadvertent IV heparin overdose.

Rationale: The evidence is insufficient for the Adult Hospital Level Committee to make a recommendation for the use of protamine in this clinical setting.

Level of Evidence: III Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

NEMLC MEETING OF 5 DECEMBER 2018:

NEMLC ratified the medicine review for protamine and accepted the recommendations as proposed by the Adult Hospital Level Committee.

Monitoring and evaluation considerations: adverse events, use: n/a

Research priorities: n/a

References:

ⁱ Pai M, Crowther MA. Neutralization of heparin activity. *Handb Exp Pharmacol*. 2012;(207):265-277.

ⁱⁱ Makris M, Hough RE, Kitchen S. Poor reversal of low molecular weight heparin by protamine. *Br J Haematol*. 2000 Mar;108(4):884-5.

ⁱⁱⁱ Massonnet-Castel S, Pelissier E, Bara L, Terrier E, Abry B, Guibourt P, Swanson J, Jaulmes B, Carpentier A, Samama M. Partial reversal of low molecular weight heparin (PK 10169) anti-Xa activity by protamine sulfate: in vitro and in vivo study during cardiac surgery with extracorporeal circulation. *Haemostasis*. 1986;16(2):139-46.

^{iv} Garcia DA, Baglin TP, Weitz JJ, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):e24S-e43S. doi: 10.1378/chest.11-2291. Review. Erratum in: *Chest*. 2012 May;141(5):1369. Dosage error in article text. *Chest*. 2013 Aug;144(2):721. Dosage error in article text.

^v van Veen JJ, Maclean RM, Hampton KK, Laidlaw S, Kitchen S, Toth P, Makris M. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis*. 2011 Oct;22(7):565-70.

^{vi} South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

^{vii} Caravati EM. Protamine sulfate. *Medical Toxicology*. 3rd ed. Dart RC, ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004;243-244