

## Who can administer

May be administered by registered competent doctor or nurse/midwife

## Important information

- Protamine is now provided in new packaging. Despite the stated neutralisation having changed from 1,000 to 1,400 units per ml the actual formulation has not changed. i.e. the **actual potency** of protamine has not changed despite the change to the **stated neutralisation**.
- Can cause anaphylactic reactions - resuscitation facilities should be available - see further information
- Very rapid administration of protamine sulphate can lead to **hypotension and anaphylactoid reactions** <sup>(ref 1)</sup>
- Excessive dosage of protamine sulphate or when given in the absence of heparin or LMWH may induce prolonged coagulation time since protamine sulphate in itself has anticoagulant activity

## Available preparations

Protamine sulphate 7,000 anti-heparin units per 5mL ampoule (50mg per 5mL)

## Reconstitution

Already in solution

**Draw up using a 5 micron filter needle**

## Infusion fluids

Sodium chloride 0.9% (volume not critical)

## Methods of intravenous administration

### Slow intravenous injection (max 5mL dose)

- Administer required dose **over approximately 10 minutes - max rate 5mg per minute** <sup>(ref 1)</sup>
- May cause **severe hypotension** if administered too rapidly

### Intermittent intravenous infusion (can be used for all doses)

- Add required dose to infusion fluid (volume not critical), and administer as a continuous infusion, adjusting rate according to aPTT response - **max rate 5mg per minute** <sup>(ref 1)</sup>

## Dose in adults

### 1. Unfractionated heparin (UFH) neutralisation

- Monitor APTT or use other tests of coagulation before starting Protamine sulphate
- If APTT is not raised, there is no indication to give/continue protamine sulphate
- 1ml (10mg) of Protamine Sulphate will neutralise approximately 1,400 units of heparin
- **Maximum dose is 50mg at any one time (i.e. 7000 units or 5mL)**

- Check APTT 5 to 15 minutes after administration of protamine
- As heparin has a relatively short half-life when given intravenously (30 minutes to 2 hours), the dose of protamine sulphate should be adjusted on the basis of the time elapsed since the intravenous administration of heparin was discontinued. **The dose of protamine in relation to the administered amount of heparin should be reduced if more than 15 minutes have elapsed since intravenous administration of heparin has stopped.**
- Once APTT is in normal range, excess bleeding risk has been neutralised
- Further doses may be needed because protamine sulphate is cleared from the blood more rapidly than heparin. An alternative is a slow constant IV infusion - adjusted to aPTT response

## 2. Low molecular weight heparins (LMWH) neutralisation

- 1mL (10mg) of Protamine Sulphate will **partially** neutralise 1,000 antiXa LMWH (higher doses than those recommended will not produce more effective neutralisation)
- The degree of neutralisation of LMWH is **product specific (in vitro studies - anti Xa neutralised = 81% for tinzaparin, 46% for enoxaparin)**
- Maximum dose is 50mg (5mL) at any one time (i.e. 7000 units or 5mL)
- **Tinzaparin:** no specific guidance provided by manufacturer
- **Enoxaparin:**
  - The dose of protamine depends on the dose of **enoxaparin** injected; 1 mg protamine neutralizes the anticoagulant effect of 100 units (1 mg) of enoxaparin, if enoxaparin **administered in the previous 8 hours**
  - An infusion of 0.5 mg protamine per 100 units (1 mg) of enoxaparin may be administered if enoxaparin was administered **greater than 8 hours previous to the protamine administration**, or if it has been determined that a second dose of protamine is required
  - **After 12 hours of the enoxaparin injection, protamine administration may not be required.** However, even with high doses of protamine, the anti-Xa activity of enoxaparin is never completely neutralized (maximum about 60%)

**Repeat administration of protamine may be required to neutralise LMWH** because:

1. Elimination is determined by the half-life of the particular LMWH used
2. Protamine sulphate is cleared from the blood more rapidly than the LMWHs
3. Absorption of LMWH after subcutaneous administration is prolonged

## 3. Cardiopulmonary bypass procedures

- Doses guided by blood coagulation studies e.g. APTT, ACT, anti-Xa

## Monitoring

- Frequent monitoring of APTT and other coagulation parameters is essential to guide treatment - see under Dose
- Anti Xa level is best for monitoring LMWH but may not always be available on an emergency basis

## Further information

- A rebound anticoagulant effect with haemorrhage has been reported occasionally despite adequate heparin inhibition by protamine sulphate
- This occurs more frequently in cases of extra-corporeal circulation in cardiovascular surgery, within 30 minutes to 18 hours after protamine sulphate administration. This rebound bleeding responds to further doses of protamine sulphate
- Excessive dosage may prolong the coagulation time because protamine sulphate in itself has

anticoagulant activity

- Hypersensitivity reactions: risk factors include: **allergy to fish, infertility in men, medical history of vasectomy, previous treatment with protamine salts**

## Storage

- Store below 25<sup>o</sup>C

## References

SPC October 2014

1: Injectable medicines guide Medusa downloaded 6th Oct 2021

## Therapeutic classification

Antidote