Drug Guideline

**Drug Guideline Title:** Urokinase – intra-arterial infusion for peripheral arterial thrombo-embolism

**Functional Sub-Group:** Patient Safety

**Summary:**
Urokinase may be used to revascularise arterial flow in lower limb thromboembolisms. The drug is not for administration in the general wards and may be initiated in radiology, with appropriate referral for patient management in a designated critical care area, with appropriate monitoring and staffing.

**Approved by:** ICU Medical Director

**Publication (Issue) Date:** January 2013

**Next Review Date:** January 2017

**Replaces Existing Drug Guideline:** 2010_Urokinase – intra-arterial infusion for peripheral arterial thrombo-embolism

**Previous Review Dates:** 2003, 2005, 2010

**Background Information:**
Patients with acute occlusion of the lower limbs may have peripheral arterial flow restored by lysing an arterial clot using the drug urokinase.

**Prescription / Approval Process**
Urokinase is not marketed in Australia. Supply is restricted under the Special Access Scheme (SAS).

- To obtain a supply of this drug, the Vascular Registrar must provide the following to the Pharmacy Department:
  - A completed SAS Category A form (available on the pharmacy dept intranet site)
  - Approval from the Director of Medical Services (DMS) on a case by case basis
  - A completed requisition form that states the name and quantity of the drug to be dispensed and identifies the patient for whom the drug is intended (i.e. has a patient identification label attached).

- It may only be dispensed for an individual patient, not as ward stock. Pharmacy generally holds enough drug to enable 24hrs of therapy. Ongoing supplies must be obtained from the manufacturer. Therefore, where possible, request supply of the drug **the day before** a planned procedure. This is especially important if the procedure is planned for a Friday. If more than 24 hrs of the drug is required the vascular registrar needs to submit another SAS form to pharmacy.

- **AFTER HOURS:** The Vascular Registrar must contact the After-Hours Hospital Manager, who obtains permission from the DMS or equivalent, and who then obtains the drug from Pharmacy.
Liverpool Hospital Intensive Care Unit

ICU Guideline: Pharmacology

Urokinase

1. Introduction contains:
The risk addressed by this drug guideline:

Clinical and patient safety

The Aims / Expected Outcome of this drug guideline:

This medication will be administered safely and potential adverse events will be minimised.

Related Standards or Legislation

NSQHS Standard 1 Governance

2. Drug Guideline: Policy Statement

- This protocol specifies the use of urokinase as an intra-arterial infusion for the treatment of peripheral arterial thrombo-embolism. For other purposes refer to the product information.
- A medical officer must prescribe all urokinase therapy. Bolus doses (if used) must be prescribed on the medication chart and infusions must be prescribed on the intravenous order/record or the ICU flowchart.
- Urokinase infusions may have a co-infusion of heparin via the arterial sheath port. This needs to be prescribed along with target aPTT by the interventional radiologist or vascular registrar (by using the “Liverpool Hospital Intravenous Heparin Chart CR 132.1”).
- This drug is not for use in the general wards. It may be commenced in the Radiology Department or Operating Theatres and the patient transferred to a critical care area for ongoing monitoring for the duration of therapy.
- The Vascular Registrar and Interventional Radiologist are to liaise with ICU for a bed post procedure. The ICU bed availability will be negotiated with the ICU outside senior registrar and ICU outside Staff Specialist.
- Ensure that the necessary IV lines, central venous access devices (CVADs) are placed prior to commencement of the procedure. These lines are to be firmly secured and observed for bleeding/disconnection.

The patient must not receive any intramuscular injections during therapy.

3. Guideline Actions

- Urokinase converts plasminogen to plasmin, which then catalyses the breakdown of fibrin, producing a systemic lytic state.
- Exact method of elimination is unknown; however elimination is decreased in chronic renal insufficiency and prolonged in hepatic insufficiency or liver cirrhosis.
- There is a distribution half life of 8 minutes and elimination half life of 48 minutes.
Indications
Within the context of this protocol the only indication is peripheral arterial thromboembolism.

Contraindications¹:
- Hypersensitivity to urokinase
- Active or recent bleeding; prior cerebral haemorrhage
- Severe uncontrolled hypertension (systolic BP > 180mmHg⁹; diastolic BP > 100mmHg or Fundus hypertonicus III & IV)
- Recent intracranial or intraspinal surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- All forms of diminished coagulability, spontaneous fibrinolysis and bleeding diatheses
- Recent (< 2 months) ‘cerebrovascular event’, stroke
- Intramuscular injection within the last 10 days

Precautions¹:
- Arterial and venous punctures should be minimized, especially at noncompressible sites
- Recent major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy
- Recent gastrointestinal or genitourinary bleeding
- Recent trauma
- High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation
- Acute pericarditis and subacute bacterial endocarditis
- Hemostatic defects
- Severe hepatic or renal dysfunction
- Pregnancy
- Diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions
- Septic thrombophlebitis or occluded arteriovenous cannula at a seriously infected site
- Patients currently receiving oral anticoagulants

Significant Interactions⁴
- Drugs affecting thrombocyte count or function e.g. acetylsalicylic acid, allopurinol, clofibrin derivatives, phenylbutazone, indomethacin, ticlopidine, para-aminobenzoic acid, dipyridamole, tetracyclines, valproic acid, thiouracil, sulphonamides, cytostatic agents, dextrans and non steroidal anti-rheumatic drugs.
- Increased risk of haemorrhage with concomitant use of anticoagulants e.g. heparin and warfarin.
- Inhibited by antifibrinolytic agents such as aprotinin, epsilon-aminocaproic acid and tranexamic acid.

Potential Adverse Effects⁴
- Common: bleeding, including bleeding at injection sites, intracerebral bleeding, internal bleeding (eg GI, genitourinary), transient hypotension
- Infrequent: allergic reactions including fever, chills, rash, nausea, headache, bronchospasm, anaphylaxis, vasculitis, nephritis
- Rare: cholesterol embolism

Treatment of Overdosage⁵
- If bleeding can be controlled by compression, treatment may continue with careful monitoring.
• However, for severe or life threatening haemorrhage with hyperfibrinolysis, administration of human fibrinogen, plasma or whole blood replacement is also indicated.

**Presentation**

- 100,000 IU /10mL vial (white lyophilisate for reconstitution with 10mL sterile water for injection)
- 500,000 IU/ 10mL vial (white lyophilisate for reconstitution with 10mL sterile water for injection)

**Administration Guidelines**

- The medical officer prescribing the drug is to review the contraindications and precautions prior to commencement of the therapy.
- The patient must have an arterial sheath inserted and the appropriate central venous access. **No IM injections should have been administered within the previous 10 days.**

**Urokinase**

- Use only a syringe driver for the infusion.
  
  **For 500,000 IU/10mL vial**
  
  Reconstitute one vial of 500,000 IU with 10mL sterile water for injection and dilute in sterile 0.9% sodium chloride to give final volume of 50mL;  
  final concentration of 500,000 IU in 50mL (10,000 units/ml)

  or

  **For 100,000 IU/10ml vial:**
  
  Reconstitute 5 vials of 100,000 IU using 10mL sterile water for injection per vial and draw up to give final volume of 50mL  
  final concentration of 500,000 IU in 50mL (10,000 units/ml)

- **Infusion rate is at 100,000 IU per hour (10mL per hour).**
  This enables a maximum of 5 hours therapy per fully loaded syringe.
  **Note:** The water jet is directed at the wall of the vial to avoid frothing. Do not shake

**N.B.**

- If the urokinase infusion requires a co-infusion of heparin via the arterial sheath port, this must be prescribed by the interventional radiologist or vascular registrar using the heparin prescription chart and target aPTT charted (by using the “Liverpool Hospital Intravenous Heparin Chart CR 132.1”).

For heparin administration guidelines please refer to the Liverpool Hospital Guideline by right clicking on the hyperlink:  
LH_PD2010_C03.27 Heparin Infusion

**The medical officer will prescribe:**

- Patient position flat with head-of-bed elevated at 30 - 45 degrees for 6 hours, keeping the leg straight.
- Patient to remain on bed rest for 8 -12 hours.
- Fluid intake to counteract contrast administration
- Special instructions, as required.
- Recom mencement of heparin anticoagulation, via venous access, 4-6 hours post removal of arterial sheath (in consultation with the Vascular Registrar).

Please refer to the ICU – Femstop femoral compression device guideline for use when removing the arterial sheath  
Clinical Issues

• Therapy endpoints are:
  → Recannalisation of the occluded artery,
  → Return of Doppler pulse signals

• Therapy may be ceased if the following occurs:
  → Complication preventing continuation of urokinase/heparin
  → Failure to lyse the clot

• Worsening of ischaemia may occur in early therapy as the proximal clot dissolves and embolises distally.

• Repeat angiogram is attended in 12 hours and again in 8-12 hours to determine response. If nil response, therapy is ceased and the patient is scheduled for surgery.

• If the clot is dissolving, therapy may continue for up to 36-48 hours followed by angioplasty.

Patient care during intra-arterial infusion of urokinase

• Ensure venous access is available; avoid venepuncture and alert staff that no IM injections are to be administered.

• Monitor vital signs, GCS, pupils and limb strength hourly and report changes, intervene as indicated.

• Monitor circulation observations hourly: assess both lower limbs for peripheral perfusion, colour, bilateral pulses, temperature, capillary return, movement and sensation.

• Intra-arterial site: monitor groin site for bleeding, swelling, oozing, pain and integrity of connections frequently and document status of site hourly. Contact the vascular registrar if there is excessive oozing from the intra-arterial puncture site. Do not remove the occlusive dressing as this may cause dislodgement / displacement of the catheter.

• Monitor patient for local or other sites of bleeding, and consider issue of bleeding with reports of pain/need for analgesia.

• Document pain score and response to analgesia hourly; report changes and obtain intervention as indicated from the medical team.

• Assess bodily fluids for signs of occult or actual bleeding, report abnormalities.

• Bloods are to be drawn from available venous access; assess aPTT 4th hourly.

• Where bleeding is suspected and there is petechial formation and/or mouth/gum bleeding; monitor fibrin degradation products (FDP) as clot formation and lysis may deplete fibrin stores, resulting in disseminated intravascular coagulation (DIC). Include fibrinogen assay and thrombin times.

• Thrombolitics are decreased/ceased (in consultation with the Vascular Registrar) when fibrinogen levels are less than (<) 1g/L = 100mg/dL – normal value is 1.5 – 4.0 g/L.

When urokinase prescription is ceased (and documented as such):

• If heparin co-infusion is being used – cease heparin infusion (via the arterial sheath) 2-6 hours prior to removing the arterial sheath; check activated clotting time (ACT) is < 200 seconds and review with M.O. for appropriate time to remove the sheath in relation to the ACT result.

• Ensure adequate oral analgesia is administered 20 minutes prior to sheath removal. Upon removal, direct pressure is applied to the puncture site for 20 minutes and then assessed for cessation of bleeding. Alternatively, the Femostop II may be used, according to the ICU guideline.

• When manual pressure is removed, or the Femostop II seals the puncture site, monitor the patient for:
  → Bleeding – ooze, leak or frank blood from puncture site
  → Bruising
→ Haematoma formation – swelling, palpable mass or newly formed bruit (suggesting non-laminar flow)
→ Inadequate distal blood flow – reduction or absence of distal foot pulses
→ Arteriovenous fistula or pseudoaneurysm formation – as detected by follow-up angiogram/Doppler flow studies.
→ Vital signs (HR, BP, RR, SpO₂, temperature), neurovascular limb observations (colour, warmth, sensation, movement, pulses) and puncture site observations bleeding/haematoma formation) are required:
  - Every 15 minutes for 1 hour,
  - Every 30 minutes for 2 hours, then
  - Hourly until the Femostop is removed.⁸

- Observations are recorded on the ICU Flowchart
- After removal of either manual pressure or the Femostop II, the site is monitored hourly for a further 4 hours for evidence of bleeding, bruising, swelling/haematoma and for distal pulses.

5. Performance Measures
Incidents are monitored and reviewed.

6. References / Links

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Endorsed by: A Prof. Michael Parr, ICU Director
Appendix: this summary is to be used in conjunction with the ICU Guideline: Femostop femoral compression device

Patient for removal of intra-arterial or venous sheath:
- PT, aPTT and platelets are within acceptable limits.
- Intensivist or surgeon has documented request for removal.
- Lie patient flat and position belt under hips, in line with puncture site.

Doctor:
- Oral analgesia 20 minutes before procedure, as required
- Clean area, release sutures.
- Inject local anaesthetic.

Nurse:
- Attach dome to compression arch, keep sterile cover in situ.
- Rotate dome clockwise to lock.
- Check dome and connections.

Femostop Preparation:
- Remove cover from dome and position 1cm above and 1cm to the side of the puncture site.
- Ensure sheath hub is clear of dome rib (withdraw sheath slightly if required).
- Compress sidearm levers on compression arch, and then thread through the belt for a snug fit.
- The arch should be level and sits squarely across the groin area.

Drugs:
- Administer analgesia and sedation as prescribed.

Removal of ARTERIAL Sheath, application of femostop:
- Inflate dome to 20mmHg above the patient's SBP while simultaneously removing the sheath.
- Removal is achieved while pressure is low and is completed when pressure is at @ 60-80mmHg.
- Continue to increase pressure until haemostasis achieved.
- Maintain this 'initial haemostasis pressure' for 2 minutes: the artery is occluded, pedal pulses are absent. Therefore, do not exceed 3 minutes.

Pressure Reduction Process and maintenance of Haemostasis:
- Reduce pressure to attain strong pedal pulse.
- Maintain pressure for 30 minutes.
- Lower pressure by 15mmHg every 15 minutes, until at 40mmHg.
- Ensure skin does not become trapped as the dome folds and pressure is being released.
- Maintain 40mmHg pressure for 30 minutes, then completely deflate the dome.
- Get patient to cough.
- If no bleeding, remove device.

If bleeding re-occurs, re-inflate to Initial Haemostasis Pressure for 2 minutes, and then recommence reduction process.

Observations:
- Monitor HR, BP, RR, SpO₂, neurovascular limb obs (colour, warmth, sensation, movement, pulses), puncture site (bleeding, haematoma?).
- Every 15 minutes for 1 hour.
- Every 30 minutes for 2 hours.
- Hourly until removal.
- Record on ICU flowchart.