DRUG GUIDELINE

Urokinase - thrombolysis of peripheral arterial thrombus

SCOPE (Area): FOR USE IN: CVS, CCU
EXCLUSIONS: Paediatrics (seek Paediatrician advice), all other areas
SCOPE (Staff): Medical, Nursing and Pharmacy

BRAND NAMES
Urok. (Special Access Scheme)

PHARMACOLOGY AND PHARMACOKINETICS
Urokinase is an enzyme produced by the kidneys and excreted in the urine; it is isolated from human kidney tissue for therapeutic use. Urokinase binds to the fibrin component of the thrombus and converts thrombus bound plasminogen to plasmin; this degrades the fibrin matrix of the thrombus. Urokinase undergoes rapid hepatic metabolism with an elimination half-life of less than 7-20 minutes; longer in patients with hepatic dysfunction. However, its effects may persist for a few hours after administration.

INDICATIONS
- Thrombolysis of peripheral arterial thrombus in critical limb ischaemia via catheter directed intra-arterial administration, in conjunction with intravenous heparin infusion.

CONTRAINDICATIONS
Absolute
- Established cerebro-vascular event (including TIA within last 2 months).
- Active bleeding diathesis.
- Recent gastrointestinal bleeding (less than 10 days).
- Neurosurgery (intracranial, spinal within last 3 months).
- Intracranial or intra-spinal trauma within last 3 months.
- Recent trauma with possible internal injuries.

Relative major
- Cardiopulmonary resuscitation within last 10 days.
- Major nonvascular surgery or trauma within last 10 days.
- Uncontrolled hypertension: greater than 180 mm Hg systolic or 110 mm Hg diastolic.
- Puncture of non-compressible vessel.
- Intracranial tumour.
- Recent eye surgery.
- Within 10 days after intra-arterial diagnostic procedure.
Relative Minor
- Hepatic failure, particularly those with coagulopathy.
- Renal insufficiency
- Bacterial endocarditis.
- Pregnancy and first 10 days post-partum
- Diabetic haemorrhagic retinopathy.
- Thrombocytopenia

PRECAUTIONS
- Seek specialist advice before considering intrathecal or epidural analgesia or anaesthesia, or lumbar puncture (risk of epidural haematoma, which may cause paralysis).
- Hypersensitivity to urokinase – review extent of reaction.

PREGNANCY AND BREASTFEEDING
Contraindicated in pregnancy and 10 days postpartum. Seek specialist advice before prescribing, information may update regularly.

DRUG INTERACTIONS
- The following medications given in combination with urokinase increase the risk of bleeding. This risk may continue for several days after discontinuation of agent depending on the duration of action of the interacting drug. If used monitor the patient for signs of bleeding,
- List should be used as a guideline only; if concerned please refer to online resources or contact Pharmacy for advice.

<table>
<thead>
<tr>
<th>Other thrombolytics</th>
<th>alteplase, reteplase, tenecteplase.</th>
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</thead>
<tbody>
<tr>
<td>Heparin and low molecular weight heparins</td>
<td>dalteparin, danaparoid, enoxaparin, heparin can be used under the strict guidance of the radiologist</td>
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<tr>
<td>Direct thrombin inhibitors</td>
<td>bivalirudin, dabigatran</td>
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<tr>
<td>Vitamin K antagonists</td>
<td>warfarin.</td>
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<tr>
<td>Factor Xa inhibitors</td>
<td>apixaban, fondaparinux, rivaroxaban.</td>
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<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>abciximab, eptifibatide, tirofiban.</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory agents</td>
<td>aspirin (can be used), diclofenac, diflunisal, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, naproxen, piroxicam, sulindac. Note: Selective NSAIDs (celecoxib, meloxicam, parecoxib) do not directly affect clotting, but increase the risk of gastrointestinal bleeding</td>
</tr>
</tbody>
</table>
**Selective serotonin reuptake inhibitors/Selective serotonin and norepinephrine reuptake inhibitors**
citalopram, dapoxetine, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, vortioxetine

**Prostacyclin analogues**
epoprostenol, iloprost, treprostinil.

**Other**
anagrelide, cilostazol, clopidogrel, dipyridamole, prasugrel, protein C concentrate (human), ticagrelor, ticlodipine, tirofiban

**Herbal medications**
Alfalfa, anise, bilberry, bladderwrack, bromelain, cat’s claw, celery, chamomile, coleus, cordyceps, dong quai, evening primrose, fenugreek, feverfew, garlic, ginger, ginkgo biloba, ginseng (american), ginseng (panax), ginseng (siberian), grape seed, green tea, guggul, horse chestnuts, horseradish, licorice, prickly ash, red clover, reishi, S-adenosylmethionine, sweet clover, turmeric, white willow

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**DOSAGE AND ADMINISTRATION**

Resuscitation equipment must be available in case anaphylaxis occurs.
For administration only

- in CVS or Critical Care Unit

Only to be prescribed by an Interventional Radiologist.

Two IV access points are required prior to commencing urokinase for the heparin infusion and for blood sampling.

Prior to thrombolysis therapy, blood clotting profile including the activated partial thromboplastin time (APTT), INR & the fibrinogen concentration, U&Es, FBE, LFTs, and Group and Hold should be determined from the current admission. INR greater than 2, or platelets less than 50,000/ml must be reported to the Interventional Radiologist.

Prior to administering urokinase, an intravenous heparin infusion (including 5000 unit intravascular bolus) is to be commenced. Prescribe on the Heparin Intravenous Infusion Chart (MR/700.3), and aim for an APTT of 50-70 sec (ensure target APTT is written on the form) provided that no coagulation deficit is identified. Heparin is required to provide adequate protection against recurrent thrombosis. The duration of heparin infusion after urokinase is ceased is decided by the Interventional Radiologist on a case by case basis.

Urokinase is administered via special multi-sidehole thrombolysis intra-arterial catheter lying near or within the thrombus only. The urokinase infusion bag and line must be clearly labelled as intra-arterial. No other medications or fluids are to be given via this line. Urokinase infusion continues until re-angiogram or as determined by the Interventional Radiologist. Urokinase intra-arterial boluses are to be prescribed on the stat section of the National Inpatient Medication Chart (MR/700.2). Urokinase intra-arterial infusions are prescribed on an infusion order chart (MR/645) with an intra-arterial route sticker attached highlighting the order is intra-arterial.
Allergic reactions such as flushing, urticaria, dyspnoea, hypotension, and rarely anaphylaxis may occur. Allergic reactions may also occur to the contrast used during angiography.

Infusion reactions such as fever, rigors, cyanosis, hypoxemia, acidosis, back pain, and nausea and/or vomiting may occur at the beginning of the urokinase infusion.

Some patients have extreme pain management issues during initial thrombolysis. It can be beneficial to have these patients assessed by the pain team.

Low dose aspirin can be co-administered if required for other conditions.

Urokinase is only stocked in the Pharmacy, and the Pharmacy must be contacted prior to use to ensure timely supply. If out of hours obtain supply from the on-call Pharmacist via the Patient Flow Coordinator. Urokinase is only available via the Special Access Scheme (SAS), and a form must be filled out for each patient outlining the maximum amount of urokinase that may be required.

See ‘Appendix 1 – CVS Nursing Procedure for Urokinase Intra-arterial Administration’ for detailed information regarding setup, equipment and procedures.

**Reconstitution:**
Reconstitute urokinase 100,000 units vials with 2 mL water for injection and 500,000 units with 10 mL water for injection. Both give a 50,000 units/mL solution. To prevent froth formation, do not shake the vial and direct water for injection to the wall of the vial.

During manufacture of an infusion bag withdraw and discard from a sodium chloride 0.9% 1L bag the same volume that is required of urokinase for the infusion.

**Optional bolus for intra-arterial thrombolysis of peripheral arterial thrombus:**
The Interventional Radiologist will determine if a urokinase bolus is required before the urokinase infusion is commenced. Boluses are to be administered by the Interventional Radiologist only.

If required a maximum of urokinase 200,000 units (4 mL) of undiluted, reconstituted solution is administered slowly by intra-arterial injection.

**Intra-arterial infusion thrombolysis of peripheral arterial thrombus:**
Dosing is varied and determined by the Interventional Radiologist, and may vary from those listed below to a maximum of 100,000 units/hr.

**Standard dosing for age less than 75 years and no extra bleeding risk:**
Urokinase 1,000,000 units in 1 L sodium chloride 0.9% by intra-arterial infusion over 12 hours (83.3 mL/hr), repeated as determined by Interventional Radiologist.

**Standard dosing for age 75 years or greater and/or extra bleeding risk:**
Urokinase 500,000 units in 1 L sodium chloride 0.9% by intra-arterial infusion over 12 hours (83.3 mL/hr), repeated as determined by Interventional Radiologist.

Select ‘Urokinase - Intra-art’ on the Alaris® LVP with Guardrails® when administering the infusion.
For unblocking AV fistulas:

Dosing is varied and determined by the Interventional Radiologist, and administration to the fistula is by the Interventional Radiologist under ultrasound. See reconstitution above.

A total of heparin 5000 units in 5 mL is administered to different parts of the fistula prior to urokinase administration.

Urokinase (undiluted, reconstituted solution) is then administered to different parts of the fistula, generally with a dose of 200,000 (4 mL) to 500,000 (10 mL) units total dose. Dwell time in the fistula is usually 1 hr, and then the urokinase is aspirated from the fistula. On occasion extra urokinase may need to be added to the fistula, but still not exceeding a total urokinase dose of 500,000 units.

HDU/CCU bed is required post procedure for adverse reaction monitoring with consideration to increase bleeding risks.

Intravenous access must be insitu and patent.

General Administration Information

- **Infusion pump:** Alaris® LVP with Guardrails®.
- **Routes of administration:**
  - Intra-arterial: Yes (injection and infusion)
  - IV injection: No
  - IV intermittent infusion: Not at BHS
  - IV continuous infusion: Not at BHS
  - IM injection: No
  - Subcut injection: No
- **Compatible/incompatible IV drugs/fluids:**
  Consult the Australian Injectable Drugs Handbook (‘Yellow book’) in your ward area. Assume all unlisted drugs and IV fluids are incompatible – contact Pharmacy for further advice.

MONITORING (INCLUDING BLOOD TESTS)

- Pre thrombolysis bloods as outlined in Dosage and Administration.
- APTTs as outlined in DRG0038 Heparin.
- Clotting profile including INR
- U&Es, FBE, LFT, Group and Hold

NURSING PRACTICE POINTS

- The patient must be in constant visual range of treating nurse during active treatment.
- The patient must remain nil orally (sips of water are permissible) throughout treatment due to increased bleeding risk and the possible need for surgical intervention in case of complications.
- The patient is nursed in bed as flat as possible and may sit up to no more than a 30 degree angle with close monitoring of the puncture site/s. Ensure two hourly pressure area care is maintained throughout – patients are able to lie on their side as long as leg is straight at site of sheath.
- Monitor continuously for any signs of bleeding during urokinase infusion, and for a three hours after ceasing. Ask patient to report any bleeding or dampness immediately. Should serious bleeding (not controlled by local pressure) occur, urokinase and any concomitant heparin or antiplatelet agents should be discontinued immediately and Medical attention sought. See DRG0030 Protamine if heparin reversal is required.
Complete visual checks of the insertion site for signs of bleeding, and or haematoma every 15 minutes for the first hour, every 30 minutes for the 4 next hours, then hourly for the remainder of the infusion. Report any evidence of haematoma formation to HMO. Stop infusion and mark boundaries with a marker.

Observe for IV malfunction including leaks at connection site, extravasation, swelling, redness or soreness every 30 minutes for the duration of the urokinase infusion.

Pedal pulses and limb observations (colour, warmth, movement, sensation and capillary return) to be recorded at baseline and every 15 minutes for the first hour, every 30 minutes for the next 4 hours, then hourly for the remainder of the infusion. Deterioration in these observations may indicate embolisation or compartment syndrome and require Medical review.

Record vital signs (BP, HR, RR, Sa02, temp) at baseline and every 15 minutes for the first hour, every 30 minutes for the next 4 hours, then hourly for the remainder of the infusion.

Record neurological observations at baseline and every 15 minutes for the first hour, every 30 minutes for the next hour, then hourly for the remainder of the infusion. Changes in neurological observations can be life-threatening and need immediate medical attention.

Monitor for allergic reactions such as flushing, urticaria, dyspnoea, hypotension, and anaphylaxis. Contact Medical staff if a reaction occurs – if severe pause the infusion first.

Monitor for infusion reactions such as fever, rigors, cyanosis, hypoxemia, acidosis, back pain, and nausea and/or vomiting (especially at the beginning of the urokinase infusion) - if severe pause the infusion first.

If accidental dislodgement of the sheath occurs apply manual compression immediately and notify the Interventional Radiologist.

Every urine sample is to be monitored for the presence of macroscopic blood (microscopic blood will be present).

Report and document pain (may indicate bleeding or embolisation).

Avoid IM injections and other invasive procedures during thrombolytic treatment, including intravenous cannulation unless intravenous access is lost; recannulation failures require minimum 10 minutes pressure.

All injections and infusions are to be labelled as per CPP0022 Labelling of Injectable Medicines and Lines.

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**ADVERSE EFFECTS**

- **Common (>1%)**
  - bleeding, including bleeding at injection sites, intracerebral bleeding, internal bleeding (e.g. gastrointestinal, genitourinary), transient hypotension.
  - Microhaematuria and bleeding from the incision channels, haematoma and seeping haemorrhage after puncture, invasive measures, intramuscular injections, trauma or recent wounds, epistaxis, and gingival haemorrhage are frequently observed. A transient increase in transaminase levels and a fall in haematocrit levels with no clinically detectable bleeding are frequently observed.

- **Infrequent (0.1–1%)**
  - allergic reactions including angioedema, fever, chills, rash, nausea, headache, bronchospasm, anaphylaxis, vasculitis, nephritis. Emboli are occasionally formed through thrombus degradation.

- **Rare (<0.1%)**
  - cholesterol embolism.

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**DRUG PRESENTATIONS, LOCATION AND STORAGE**

Urokinase 100,000 unit and 500,000 unit vials.

Imprest Locations (at the time of guideline development): Pharmacy only.

Store below 25°C. Protect ampoules from light.
RELATED DOCUMENTS
SOP0001 Principles of Clinical Care.
CPP0549 High Risk Medications.
DRG0038 Heparin.
DRG0030 Protamine.
CPP0222 Labelling of Injectable Medicines and Fluids.

REFERENCES

Appendix 1 – CVS Nursing Procedure for Urokinase Intra-arterial Administration

Equipment Required:
- Special Access Scheme (SAS) form for urokinase
- Infusion order chart (MR/645) highlighted for intra-arterial use for urokinase, and urokinase obtained from Pharmacy, including enough to last out of hours
- Heparin Intravenous Infusion Chart (MR/700.3) for heparin
- Peripheral angiogram pack
- Urokinase 500,000 units vials x 2
- Heparin 25,000 units in 250 mL premixed bag
- Heparin 5000 units/ 5 mL
- Midazolam 5 mg/5 mL
- Fentanyl 100 microg/2 mL
- 1 L bottle sodium chloride 0.9% for irrigation
- 1 L bag sodium chloride 0.9%
- 100 mL sodium chloride 0.9% minibag
- Optiray 350 contrast 50 mL
- Chlorhexidine skin prep
- Multiple IV 30000s (for securing sheath, catheter and lines)
- 5F sheath
- 5F end-hole and side holes catheter
- Benson Wire
- Micropuncture Introduction Set
- 2x IV access with minimum volume extension tubing for possible sedation
- Alaris pump with 2 LVP modules
- Giving sets x 2 (dead space 18 mL)
- Appropriate route additive and line labels for all bags and syringes
- Consult with treating Interventional Radiologist for additional requirements

**Pre-Procedural:**
- Nursing assessment for interventional vascular angiography procedure requiring sedation should be undertaken
- Ensure there are no contraindications to urokinase or heparin administration
- Obtain informed written consent
- Complete correct procedure form
- Patient should be fasted preferably 4 hours pre-procedure
- Ensure Pathology tests as outlined above are available
- IV access x2 obtained
- Ensure analgesia/sedation available
- Full monitoring, including ECG, SpO2, blood pressure, respiration rate and temperature is required
- Intranasal oxygen administration only required if clinically indicated

**Procedure:**
Patient positioned on the cardiovascular suite table according to required access. The patient is and prepped with chlorhexidine (unless known allergy, then betadine is to be substituted) and draped in a sterile fashion. The appropriate Surgical Time Out is to be performed, including patient ID checks and consent. Intra-operative intravenous sedation/pain relief medications given if required and ordered by the interventional radiologist. The interventional radiologist will gain arterial access and an appropriate sheath inserted. The occluded vessel is identified and the catheter through which the urokinase infusion is to be administered, positioned. The catheter and sheath are carefully secured with IV 3000s. Continuous monitoring as described above is to be maintained and monitored for adverse reaction, including vaso-vagal reactions in response to arterial access.

**Medications Required:**
Always refer to and consult relevant medication preparation guide

Midazolam
Fentanyl
Heparin
Urokinase