SESLHD GUIDELINE COVER SHEET

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KEY TERMS	Urokinase Administration
SUMMARY	The guideline has been established to standardise the administration of urokinase in specific clinical areas. Administration of urokinase is limited to the Operating Theatres, Intensive Care/High Dependency Units and the Medical Imaging Departments (MID) at St George Hospital (SGH) and Prince of Wales Hospital (POWH).

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Administration of Urokinase in Specific Clinical Areas

Section 1 – Background

Urokinase is a thrombolytic drug extracted from human urine. It directly converts plasminogen to form plasmin, the proteolytic enzyme responsible for the breakdown of fibrin into small peptide molecules. It is used to eradicate vascular occlusions which can be the result of an embolus or an acute thrombosis.

Section 2 – Principles

Acute limb ischaemia due to an embolus or thrombus requires rapid diagnosis and initiation of treatment if permanent damage is to be avoided. Treatment may involve catheter directed intra-arterial or intra-venous thrombolytic therapy or surgery.

Before starting thrombolytic therapy, haemostasis tests should be performed including haematocrit, platelet count, thrombin time (TT) and activated partial thromboplastin time (APTT).

Urokinase should only be used by physicians experienced in the management of thrombotic diseases in hospitals where adequate diagnostic and monitoring techniques are available.

Administration of urokinase is limited to Operating Theatres, Intensive Care/High Dependency Units and the Medical Imaging Departments (MID) at St George Hospital (SGH) and Prince of Wales Hospital (POWH). The referring Medical Officer (MO) must arrange for a bed in the Intensive Care/High Dependency Units.

Section 3 – Definitions

- AF - Atrial Fibrillation
- APTT - Activated Partial Thromboplastin Time
- ATE - Arterial Thromboembolism
- CPR - Cardio Pulmonary Resuscitation
- CVA - Cerebral Vascular Accident
- FBC - Full Blood Count
- GCS - Glasgow Coma Scale
- HDU - High Dependency Unit
- IA - Intra-arterial
- IV - Intravenous
- MID - Medical Imaging Departments
- MO - Medical Officer
- Nomogram - A graphic representation of numerical relations
- OT - Operating Theatres
- POWH - Prince of Wales Hospital
- PT - Prothrombin Time
- RN - Registered Nurse
- SGH - St George Hospital
- TGA - Therapeutic Goods Administration
- VTE - Venous Thromboembolism

Section 4 – Indications

This protocol specifies the use of urokinase as an intra-arterial or intra-venous thrombolytic therapy for the treatment of peripheral thrombo-embolism.

Section 5 – Contraindications and/or Precautions

If any signs or symptoms of adverse reaction develop, the infusion is to be stopped immediately and medical assistance called for.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Active clinically relevant bleeding
- Aneurysm and arteriovenous malformation
- Intracranial neoplasm or other neoplasm with risk of haemorrhage
- Decreased blood coagulation (haemorrhagic diathesis, concomitant therapy with anticoagulants, spontaneous fibrinolysis) and severe thrombocytopenia
- Severe uncontrolled arterial hypertension (systolic > 200 mmHg, diastolic > 100 mmHg; grade III or IV hypertensive retinopathy)
- Acute pancreatitis, pericarditis, bacterial endocarditis, sepsis
- Recent cerebrovascular accident (e.g. within two months)
- Recent trauma including cardiopulmonary resuscitation, thoracic surgery or neurosurgery (e.g. within two months)
- Recent major surgery until primary wound healing, recent organ biopsy, lumbar puncture, translumbal aortography (e.g. within 10 days)

Precautions

In the following conditions, the risk of bleeding may be increased and should be weighed against the anticipated benefits:

- Recent severe gastrointestinal bleeding
- Recent surgery other than thoracic or neurosurgery, recent obstetrical delivery, puncture of non-compressible vessels
- Moderate coagulation defects including those due to severe hepatic or renal diseases
- Cavernous pulmonary diseases
- Genitourinary tract diseases with existing or potential sources of bleeding (e.g. implanted bladder catheter)
- High likelihood of a left heart thrombus (e.g. mitral stenosis with atrial fibrillation) with possible risk of cerebral embolism
- Known septic thrombotic disease
- Severe cerebrovascular disease
- Elderly patients (especially those over 75 years)
- Due to increased risk of haemorrhage, concomitant use of urokinase and active substances that affect platelet function (e.g. aspirin, other non-steroidal anti-inflammatory agents, dipyridamole, dextrans) should be avoided.

Adverse Effects

Haemorrhage

The most frequent and severe adverse effect of urokinase therapy is haemorrhage. The haemostatic status of the patient may be more profoundly altered with urokinase therapy than with heparin or coumarin-derivative anticoagulant therapy.

Severe spontaneous bleeding, including fatalities resulting from cerebral haemorrhage, has occurred during urokinase therapy. Less severe spontaneous bleeding has occurred approximately twice as frequently as that occurring during heparin therapy. Patients with pre-existing haemostatic defects have the greatest risk of spontaneous bleeding.

Retroperitoneal Haematoma, an accumulation of blood found in the retroperitoneal space, is a major risk.

Hypersensitivity reactions

In contrast to streptokinase, urokinase is reportedly non-antigenic. However, mild allergic reactions including bronchospasm and rash have been reported rarely. In addition, very rare cases of fatal anaphylaxis have been reported.

Infusion reactions

Fever and chills, including shaking chills (rigors), have been reported occasionally in patients receiving urokinase. Symptomatic treatment is usually sufficient to alleviate discomfort caused by urokinase-induced fever; however, aspirin or non-steroidal anti-inflammatory drugs should not be used.

Other infusion reactions reported with urokinase therapy include dyspnoea, cyanosis, hypoxemia, acidosis, back pain, and nausea and/or vomiting; these effects/reactions generally occurred within one hour of beginning urokinase infusion.

Overdose

Haemorrhage that occurs during treatment with urokinase may be controlled with local pressure and treatment continued. If severe bleeding occurs, treatment with urokinase must be stopped and inhibitors such as aprotinin or tranexamic acid can be given. In serious cases, human fibrinogen, factor XII, packed red cells or whole blood should be given as appropriate. For correction of volume deficiency, dextrans should be avoided.

Fluid Overload- Hypervolemia

Complication arising from pre-existing cardiorespiratory disease and severe acute illness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are required to report any suspected adverse reactions via IIMS and the Therapeutic Goods Administration (TGA).

Section 6 – Process

In addition to the following processes, all relevant policy directives must be adhered to when prescribing, preparing and administering urokinase infusion.

6.1 Patient Preparation

Consent is required as per NSW Health Consent to Medical and Healthcare Treatment Manual 2020 and using Consent for Exceptional Use of Medicines Form SEI020.025.

Urokinase is not registered for use in Australia and hence requires a special access scheme (SAS) form to be completed by the senior proceduralist or a **Senior** Medical Officer from the admitting medical team prior to obtaining supplies.

Pathology required prior to administration of urokinase - full blood count (FBC), fibrinogen, prothrombin time (PT) and activated partial thromboplastin (APTT).

The referring Medical Officer (MO) must arrange for a bed in the Intensive Care/High Dependency Units.

6.2 Medical Imaging Department/Operating Theatre Responsibilities

- Proceduralists must confirm correct patient, correct procedure and correct site according to NSW Ministry of Health Policy - PD2014_036 Clinical Procedure Safety
- A femoral angiogram is attended, a sheath is inserted
- Heparin infusion via access sheath (side arm)
- Urokinase infusion via infusion catheter (long catheter inserted through the access sheath)
- The first dose of urokinase is loaded and commenced in the Medical Imaging Department/Operating Theatres
- Further doses are to be written up by the treating team.

6.3 Preparation of Urokinase Infusion

Table 1:

Urokinase Process

Urokinase dose and infusion rate must be ordered by the Senior Proceduralist on a **separate Fluid** Order Chart (i.e.other fluids or medications **must not** be ordered on this chart).

- Urokinase is obtained from the pharmacy
- One vial of 500,000 units urokinase is to be reconstituted with 10mL of water for injection (do not shake vigorously to avoid frothing)
- After reconstitution the solution must be clear and colourless
- Reconstituted solution of urokinase is then added to 500mL of sodium chloride 0.9% solution, resulting in a final concentration of 1000 units/mL
- Label the infusion bag in accordance with NSW Ministry of Health Policy - PD2016_058 User applied Labelling of Injectable Medicines, Fluids and Lines
- Administer via an infusion pump
- Intra-arterial line labels must be placed on the line as per NSW Ministry of Health Policy - PD2016_058 User applied Labelling of Injectable Medicines, Fluids and Lines
- The urokinase infusion is usually administered at a rate of 80,000 units – 100,000 per hour as prescribed by senior proceduralist
- The total dose per treatment ranges from 500,000 units up to four million units of urokinase
- If the urokinase infusion requires a co-infusion of heparin via the arterial sheath port, this must be prescribed by the treating Medical Team.

6.4 Commencement of Urokinase Infusion

- The urokinase infusion is commenced by the senior proceduralist
- A bolus dose of urokinase **may** be administered by the senior proceduralist prior to commencing the infusion. This must be recorded on the Fluid Order Chart.
- The urokinase infusion **must** be administered via an infusion pump. Staff must ensure that the infusion is kept running **at all times**.
- If a sheath has been used, this must also be kept patent with a **separate continuous infusion of heparin**.
    - Usually 500ml of sodium chloride 0.9% loaded with 5,000 units of heparin is administered at 50 ml per hour via the sheath. This is required to prevent peri-catheter thrombosis formation, distal clot propagation and rethrombosis proximal to the catheter tip during thrombolysis infusion.
- The sheath and the catheter should be clearly labelled as " Arterial Sheath", "Arterial Catheter" or "Venous Sheath", "Venous Catheter "
- Prior to transfer to ICU/HDU, the nursing and medical staff must ensure there is sufficient volume of the urokinase infusion remaining in order to run at least another hour
- In the event that the urokinase infusion is stopped, both the catheter and sheath must remain patent using either a sodium chloride 0.9% or a sodium chloride 0.9% with heparin infusion, administered via an infusion pump as per instruction from Medical Officer
- If the senior proceduralist wants anticoagulation in addition to that running through the sheath, this must be clearly documented in the post procedural instructions, and be prescribed by the proceduralist in consultation with intensive care staff.

6.5 Post Procedure Care

6.5.1 General

- The patient transferred to ICU/HDU
- Patient to be reviewed by ICU consultant
- Patients IV fluid intake to be assessed by treating medical team
- Patient may eat and drink as ordered
- A strict fluid balance chart must be maintained
- Medications to be reviewed and taken as ordered by the treating medical team
- Central lines **must not** be inserted until the patient has a full recovery of normal coagulation for review from ICU consultant
- **NO** intramuscular injections are to be administered until the patient has a full recovery of normal coagulation
- Check that all infusion connections are secure and running **at all times**
- Review angiography report for instructions – nursing and medical entries
- Patients must remain on strict bed rest
- Head of bed may be elevated to 30 degrees.
- A check angiogram is scheduled within 24 hours of the initial procedure to assess the progress of thrombolysis. Clearance of thrombosis can take from four to 18 hours. The treating medical team will arrange the follow up angiogram.

6.5.2 Observations

a) Blood pressure/heart rate/respiratory rate/SpO_2 and Neurovascular observations of vascular puncture site for bleeding and swelling/assessment involves assessing the pulses, colour, temperature, movement and sensation of the extremity.

- Every 15 minutes for two hours
- Every 30 minutes for two hours
- Hourly for eight hours
- Four hourly for 24 hours, **after 24 hours - every shift until discharged**

b) Neurological Observation Glasgow Coma Scale (GCS) attended every four hours

c) Urinalysis must be attended and recorded every four hours. Urine must be checked for the presence of blood

d) An accurate stool chart must be maintained. Faeces must be checked for the presence of blood.

6.5.3 Pathology

- Daily and PRN fibrinogen, activated partial thromboplastin time (APTT), prothrombin time (PT) and FBC must be ordered and attended. It is the responsibility of the admitting medical team to follow up pathology results.
- Note there is no reliable correlation between the severity of clinical bleeding complications and the degree of derangement of any of the coagulation/haemostasis tests. A normal test result does not preclude bleeding. Attending medical team to review patient.

6.5.4 Sheath/Catheter Removal

- Sheaths should only be removed by suitably experienced personnel
- PT, APTT and platelets are within acceptable limits
- Intensivist or surgeon has documented request for removal.

Theatres

- The sheath removal can occur in theatre by the vascular surgeon when a closure device is used
- The heparin infusion does not have to stop due to the risk of rethrombosis of the vessel.

Radiology

- At the completion of urokinase infusion, the radiologist will usually remove the catheter during the follow up angiogram, leaving the sheath insitu.

ICU/HDU

- The urokinase infusion must be ceased for at least two hours prior to sheath removal
- Systemic IV Heparin infusion should be stopped two hours prior to sheath removal
- IV heparin should be recommenced as per treating team 60 minutes after sheath removal, without a bolus heparin injection
- The sheath must be kept patent until removal using either an infusion of sodium chloride 0.9% or sodium chloride 0.9% with heparin
- Stop sheath heparin infusion 90 minutes prior to sheath removal
- Recommence systemic IV heparin infusion 60 minutes after removal.

6.5.5 Troubleshooting

- If catheter or sheath becomes dislodged or pulled out 5cm or more, patient **must immediately** be reviewed by the admitting medical team
- The patient may need to return to angiography for replacement/repositioning of the catheter/sheath
- If swelling or bleeding occurs at the insertion site, apply pressure just above the catheter entry point for at least 25 minutes, and seek medical advice immediately.

6.6 Removal of Arterial Sheath and Venous Sheath

6.6.1 Options for achieving haemostasis:
Arterial Sheath

a) Manual pressure

- Pressure over the puncture site with gloved fingers. Sufficient pressure to be able to feel the underlying femoral pulse, not so much pressure that the distal pulse is obliterated. Typically takes 10-15 minutes to achieve haemostasis.

b) Arterial Clamp Device

- Follow manufacturer's instructions for deployment.

Venous Sheath

a) Manual pressure

- Pressure over the puncture site with gloved fingers. Sufficient pressure to achieve haemostasis. Typically takes 10-15 minutes.

Section 7 – References

NSW Ministry of Health Information Bulletin IB2020_010 – Consent to Medical and Healthcare Treatment Manual
NSW Ministry of Health Policy Directive PD2016_058 - User-applied Labelling of Injectable Medicines, Fluids and Lines
NSW Ministry of Health Policy Directive PD2013_043 - Medication Handling in NSW Public Health Facilities
NSW Ministry of Health Policy Directive PD2017_032 - Clinical Procedure Safety
SESLHDPR/402 - Heparin - Anticoagulation with Intravenous Heparin Sodium Infusion (Adults)
Angiography Arterial Puncture Neurovascular Observation Chart SES110.028

External references

SHPA Australian Injectable Drugs Handbook, 6th Edition
Therapeutic Goods Administration
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Urokinase medac. Product information. Hamburg, Germany. Medac GmbH. 04/2015
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Section 8 – Revision and Approval History

Date	Revision no:	Author and approval
February 2016	Draft	Andrewina Piazza-Davies, SESLHD Clinical Stream Nurse Manager, Surgery, Anaesthetics, Peri-Operative
March 2016	Draft	Draft for Comment – four weeks Kim Clinen, Clinical Nurse Educator, Medical Imaging Department , St George Hospital
March 2016	Draft	Draft for Comment – further two weeks
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November 2016	1	Endorsed by SESLHD Clinical and Quality Council
December 2016	1	Changes made concerning dosage for review and approval by SESLHD Quality Use of Medicines Committee
March 2017	1	Endorsed by SESLHD Quality Use of Medicines Committee
May 2018	2	Minor review undertaken, updates endorsed by Executive Sponsor
July 2018	2	Endorsed by SESLHD Quality Use of Medicines Committee
September 2020	3	Minor review. Executive Sponsor and author contact information updated. Links and references updated. Approved by Executive Sponsor.