Protocol for Administering Alteplase in Acute Ischaemic Stroke

Neurosciences and the Senses Health Network
February 2011

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Links to:	Stroke Model of Care for WA

1.1 Summary section

The Neurosciences and the Senses Health Network's Model of Stroke Care for WA,[1] under the Clinical Lead of Professor Bryant Stokes, was endorsed by the State Health Executive Forum (SHEF) at the WA Department of Health in February 2006.

Stroke, as described in the Model of Stroke Care,[1] can be caused by a ruptured vessel in the brain or blockage of brain by blood clot. The treatment usually occurs in two phases. The first phase involves immediate steps to save the patient's life. This sometimes involves dissolving the blood clot; the most effective substance currently available for this step is tissue plasminogen activator (alteplase).[1] In order to be effective, alteplase must be given as soon as possible (up to a maximum of four and half hours) after stroke onset.[1] This drug may dissolve thrombus, restoring the flow of blood to the brain.[2]

Once a patient's condition is stabilised, the second phase of the treatment begins which is the rehabilitation stage.

Through developing the Model of Stroke Care,[1] the Neurosciences and the Senses Health Network (NSHN) identified the need to provide information and support on stroke management at a state-wide policy level. This supporting operational guideline for the recommended 'tissue plasminogen activator' is endorsed and will be operational within the major stroke units in WA.

In WA, the approved centres for alteplase are currently: Fremantle Hospital, Royal Perth Hospital (RPH), Sir Charles Gairdner Hospital (SCGH) and Swan Districts Hospital. This guideline has been compiled from standard practice documents used in the above hospitals.

There was close liaison with the guideline development team, and the NSHN during the review process and development of this policy.

Other country and metropolitan hospitals are encouraged to review this protocol and seek to implement the necessary medical, imaging, nursing, pharmacy, laboratory and other procedures before using alteplase in ischaemic stroke.

This document will be reviewed regularly. Your comments and feedback regarding this document are welcomed and can be directed to Associate Professor David Blacker (Neurologist SCGH) and Clinical Professor Peter Silbert (State Director of

Neurology) on the health department global email system.

1.2 Aim/objective

The guideline aims to:

- Provide evidence based practice guidelines for stroke care.
- Support early intervention in stroke management and develop a consistent state-wide approach to stroke care.
- Encourage stronger alignment of the strategic and operational functions of stroke care in WA, with the best practice recommendations of the WA Stroke Model of Care. [1]

The guideline is designed for health professionals with the authority to administer alteplase. Such health professionals must be acting under the advice of a specialist physician and an interdisciplinary acute care team, with expert knowledge in stroke management. The guideline also provides pathways and protocols to help guide medical, nursing and allied health professionals in acute-phase management.

1.3 Scope

The administration of alteplase is appropriate only for patients suffering ischaemic stroke if the onset is within the preceding 4.5 hours in select cases. The clinical guideline outlines the full eligibility criteria for application of alteplase.

The guideline applies to acute stroke units/services, emergency departments (ED), intensive care units (ICU), and hospital medical advisory committees.

1.4 Introduction

The most effective substance currently available for dissolving blood clots immediately following the onset of ischaemic stroke is tissue plasminogen activator (alteplase). In order to be effective alteplase must be administered as soon as possible (up to a maximum of 4.5 hours) after the onset of the stroke.[3] The drug aims to dissolve thrombus, restoring the flow of blood to the brain.[3] The alteplase clinical guideline outlines the assessment for acute stroke, the eligibility criteria for alteplase, directions for care, and counseling for patients and families post-stroke.

1.5 Definitions

- **Stroke:** The sudden death of cells in a limited part of the brain caused by a reduced flow of blood to the brain. A stroke can be caused by a ruptured blood vessel in the brain (intra-cerebral haemorrhage) or a blockage of the brain blood clot (ischaemic stroke).[4]
- **Tissue plasminogen activator (alteplase):** A drug which acts to dissolve the blood clot that is causing the ischaemic stroke.[2]
- **Transient Ischaemic Attack (TIA):** A mini-stroke caused by temporary disturbance of blood supply to an area of the brain which results in a sudden, brief decrease in brain function.[5]

2 Methodology

A working group of relevant experts was formed to develop the guideline. The group used the following method.

- Review of existing alteplase Australian guidelines and standard practice documents from RPH, SCGH and Swan Districts Hospital.
- Review of alteplase guideline literature from USA and Europe.
- Where appropriate, local practice guidelines were used (such as bladder management and early mobilisation guidelines).
- Expert opinion to supplement available evidence.

2.1 Endorsements and approvals

- The WA Stroke Focus Group
- The NSHN, Neurosciences Advisory Group Subcommittee
- The Neurological Interventional and Imaging Service of Western Australia.

2.2 Guideline team

Assoc Prof David Blacker	Neurologist, SCGH
Clinical Professor Peter Silbert	State Director of Neurology/ Neurologist
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3 Acknowledgements

- Health Networks, Department of Health WA
  - Neurosciences and the Senses Health Network (NSHN)
  - Neurosciences Advisory Group
  - Andrew Jones, Senior Development Officer
  - Pranita KC, Development Officer.
- Western Australian Focus Group
- The medical, nursing and pharmacy staff from RPH, SCGH, Fremantle Hospital, and Swan Districts Hospital who contributed significantly to this work**.**

3.1 Companion documents

- The Model of Stroke Care for Western Australia[1]
  http://www.healthnetworks.health.wa.gov.au/modelsofcare/docs/Stroke_Model_of_Care.pdf
- Clinical Guidelines for Acute Stroke Management[6]
  http://www.strokefoundation.com.au/acute-clinical-guidelines-for-Acute-stroke-management

  "Intravenous alteplase in acute ischaemic stroke must only be given under the authority of a specialist physician and interdisciplinary acute care team with expert knowledge of stroke management, experienced in the use of thrombolytic therapy and with pathways and protocols available to guide medical, nursing and allied health acute phase management. Pathways or protocols must include guidance in acute blood pressure management."[6]

3.2 Links

- National Stroke Foundation
  www.strokefoundation.com.au
- Stroke Society of Australasia
  www.strokesociety.com.au

4 Emergency Department assessment of acute stroke

4.1 Triage

If a patient presents with any of the symptoms below, ***with a duration of less than 4 hours*** and an acute stroke is suspected, the patient should be triaged as Level 2.

Sudden onset of any of the following symptoms:

- Facial weakness
- Arm weakness
- Speech disturbance (Aphasia/Dysarthria)
- Hemiparesis or hemisensory disturbance
- Ataxia
- Diplopia / visual loss.

ACTION

- ***Patient must be seen by a doctor within 10 minutes.***
- ***Call stroke or neurology medical staff according to hospital protocol (Appendix E).***

OR

- ***Call 55 and state "stroke team required".***

4.2 Emergency team staff

- "ABCs".
- Contact stroke or neurology team early to assist in / facilitate acute management.
- Vital signs: temperature, blood pressure, heart rhythm and rate.
- Order urgent plain computerised tomography (CT) head scan.
- IV access- FBP, finger-prick glucose, COAGS, BSL, U+E, Group and hold. (Only results of platelet count and BSL are required prior to administration, ***unless the patient is on warfarin***).
- ECG (do not delay CT for this).
- Consider CXR but do not delay CT or alteplase.
- Communication of finger-prick glucose result to stroke or medical registrar.
- Ask family to stay and be available to stroke team.
- Urinary indwelling catheters (IDC) are inserted at the discretion of the treating stroke consultant.
- Nasogastric tubes are ***not*** recommended prior to thrombolytic therapy, unless there are strong clinical indications.

4.3 Stroke team staff

- Confirm time of onset and review history.
- Review checklist for thrombolysis eligibility (page 12 of this document).
- Focussed neurological examination using National Institutes of Health Stroke Scale (NIHSS - modified version).
- Accompany patient to CT and continue assessment if necessary.
- Review CT scan with radiology staff and immediately discuss with stroke consultant.

All cases must be discussed with the admitting stroke consultant before proceeding.

- If suitable for intravenous alteplase (tissue plasminogen activator), then return to ED resuscitation area.
- If uncertain of benefit-to-harm ratio of alteplase (e.g. age > 80 years, NIHSS score < 4 or > 25, vertebro-basilar territory ischaemic stroke, prior stroke within last 3 months) and time is 0-6 hours since onset of acute ischaemic stroke, seek consent from patient or next of kin for randomisation in International Stroke Trial 3 (IST-3) (if ethics approval available at your hospital).
- If certain that benefit to harm ratio of alteplase favours alteplase, administer as per IV alteplase protocol.
- After administration of alteplase, the patient should be transferred to the Stroke Unit, High Dependency Unit (HDU) or the ICU depending on nursing availability to provide required frequent observations.
- Alteplase is licensed for use in appropriate patients with symptom duration up to 4.5 hours. Cases of acute basilar thrombosis may be treated with intra-arterial thrombolysis up to 24 hours from symptom onset due to the devastating nature of this condition.
- Intra-arterial thrombolysis and mechanical clot extraction techniques may also be an option in cases of stroke after recent surgery (< 14days), coronary angiography, pregnancy, and in cases of severe basilar thrombosis not responding to IV alteplase (i.e. “rescue”). Discuss with interventional neuroradiologist.

  The Neurological Intervention and Imaging Service (NIIS) of WA - a state based service for advanced neuro-imaging and intervention based at SCGH and RPH. The Service works closely with neurology services and can be contacted on 93464455 at SCGH or 92241069 at RPH.

5 Eligibility criteria for IV alteplase within 4.5 hours of stroke onset

5.1 Patient selection criteria [3,7]

Alteplase indications

1. Onset of ischaemic stroke within the preceding 4.5 hours, measurable and clinically significant deficit (>4) on NIHSS.
2. Patient's CT does not show haemorrhage or non-vascular cause of stroke.

   (Subtle signs of ischaemia on CT scan are not an absolute contra-indication to alteplase but may be associated with an increased risk of intracranial haemorrhage with alteplase treatment.)

3. Patient's age is >18 years.

Alteplase contraindications – ABSOLUTE [3,7]

Do NOT administer alteplase if any of these statements are true:

1. Uncertainty about time of stroke onset (e.g. patients awakening from sleep).
2. Coma or severe obtundation with fixed eye deviation and complete hemiplegia.
3. Hypertension: systolic blood pressure ≥ 180mmHg; or diastolic blood pressure >110mmHg on repeated measures prior to study. (If treated, see appendix A, patient can become eligible again.)
4. Clinical presentation suggestive of subarachnoid haemorrhage even if the CT scan is normal.
5. Presumed septic embolus.
6. Patient having received a heparin medication within the last 48 hours and has an elevated Activated Prothrombin Time (APTT) or has a known hereditary or acquired haemorrhagic diathesis (e.g. INR or APTT greater than normal). Known lupus anticoagulant is not a contraindication to alteplase.
7. INR >1.5[7] Known advanced liver disease, advanced right heart failure, or anticoagulation, and INR > 1.5 (no need to wait for INR result in the absence of the former three conditions).
8. Known platelet count <100,000 uL.
9. Serum glucose is < 2.8mmol/l or >22.0 mmol/l.

5.2 Relative Contraindications [3,7]

If any of the following statements are true, use alteplase with caution. In each situation below, careful consideration of the balance of the potential risks and benefits must be given.

1. Severe neurological impairment with NIHSS score >22.
2. Age >80 years.
3. CT evidence of extensive middle cerebral artery (MCA) territory infarction (sulcal effacement or blurring of grey-white junction in greater than 1/3 of MCA territory).
4. Stroke or serious head trauma within the past three months where the risks of bleeding are considered to outweigh the benefits of therapy.
5. Major surgery within the last 14 days (consider intra-arterial thrombolysis).
6. Patient has a known history of intracranial haemorrhage, subarachnoid haemorrhage, known intracranial arteriovenous malformation or previously known intracranial neoplasm such that, in the opinion of the clinician, the increased risk of intracranial bleeding would outweigh the potential benefits of treatment.
7. Suspected recent (within 30 days) myocardial infarction.
8. Recent (within 30 days) biopsy of a parenchymal organ or surgery that, in the opinion of the responsible clinician, would increase the risk of unmanageable (e.g. uncontrolled by local pressure) bleeding.
9. Recent (within 30 days) trauma with internal injuries or ulcerative wounds.
10. Gastrointestinal or urinary tract haemorrhage within the last 30 days or any active or recent haemorrhage that, in the opinion of the responsible clinician, would increase the risk of unmanageable (e.g. by local pressure) bleeding.
11. Arterial puncture at non-compressible site within the last 7 days.
12. Concomitant serious, advanced or terminal illness or any other condition that, in the opinion of the responsible clinician would pose an unacceptable risk.
13. Rapidly improving deficit.
14. Seizure: If the presenting neurological deficit is deemed due to a seizure, do NOT give alteplase. If the presenting neurological deficit is related to ischaemia, consider alteplase as per protocol.
15. Pregnancy is not an absolute contraindication. Consider referral for intra-arterial thrombolysis.

6 The Modified National Institutes of Health Stroke Score

Table 1 The Modified National Institutes of Health Stroke Score

Item Number	Item Name	Scoring Guide	Patient Score
1B	LOC* questions *What is your age?* *What month is it?*	0=both correct 1=one correct 2=neither correct	
1C	LOC commands *Grip my hand.* *Open/close your eyes.*	0=both correct 1=one correct 2=neither correct	
2	Gaze	0=normal 1=partial palsy 2=total palsy	
3	Visual fields	0=no visual loss 1=partial hemianopia 2=complete hemianopia 3=bilateral hemianopia	
5A	Left arm motor *Hold your arms up, 90° sitting or 45° supine.*	0=no drift 1=drift <10 sec 2=falls <10 sec 3=no effort against gravity 4=no movement	
5B	Right arm motor	0=no drift 1=drift <10 sec 2=falls <10 sec 3=no effort against gravity 4=no movement	
6A	Left leg motor *Lift your leg up, to 30°.*	0=no drift 1=drift <10 sec 2=falls <10 sec 3=no effort against gravity 4=no movement	
6B	Right leg motor	0=no drift 1=drift <10 sec 2=falls <10 sec 3=no effort against gravity 4=no movement	
8	Sensory	0=normal 1=abnormal	
9	Language	0=normal 1=mild aphasia 2=severe aphasia 3=mute, or global aphasia	
11	Neglect	0=normal 1=mild 2=severe	

*LOC= level of consciousness **TOTAL** (out of 31) _____

Modified National Institutes of Health Stroke Scale for use in Stroke Clinical Trials [8]

A score of 4 or more is considered to represent a clinically significant deficit. A score of more than 20 is considered a severe stroke. In the National Institute of Neurological Diseases and Stroke (NINDs) trial of alteplase, the risk of intracranial haemorrhage was 3% in patients with a score of less than 10, but 17% in patients with a score 20 or greater.

6.1 Alteplase administration for acute ischaemic stroke

This protocol applies to the use of alteplase for acute ischaemic stroke only. For other indications consult other literature.

Category: Thrombolytic

Trade Name: Actilyse

Presentation: 50mg and 10mg vial with diluent

Reconstitution

- Alteplase should be reconstituted to a concentration of ***1mg/mL***.
- Use only the diluent (sterile water for injections) provided for reconstitution.
- Dissolve by gentle agitation to prevent excess foaming.
- Reconstitute 50mg vial with 50mL or 10mg vial with 10mL of diluent using the transfer cannula provided. The transfer cannula must be introduced vertically into the rubber stopper and through the mark at its centre. Alternatively, a large bore 18 gauge needle can be used.
- Slight foaming upon reconstitution is not unusual. Excessive or vigorous shaking should be avoided.
- For patients > 55kg use a combination of 50 mg and 10 mg vials to avoid wastage.

Dose

The recommended dose is ***0.9mg/kg bodyweight.*** This dose is given in 2 parts:

(i) 10% of the total dose is administered as an IV bolus, followed immediately by

(ii) the remaining dose added to 50mL sodium chloride 0.9% minibag and administered as an IV infusion over 60 minutes.

The total dose of alteplase used for the treatment of acute ischaemic stroke should not exceed 90mg.

1. Identify approximate weight of the patient. Use dosing table to obtain total dose. Maximum dose: 90mg.
2. Reconstitute alteplase as above. Withdraw bolus dose – this dose is given as an IV push over 1 minute.
3. Withdraw infusion dose and add dose to 50mL sodium chloride 0.9% minibag – this infusion is given over 60 minutes via a volumetric control pump e.g. Hospira Plum A infusion pump. Prime the tubing carefully with alteplase solution. Do not prime the tubing with 0.9% sodium chloride.
4. Flush line with 30mL 0.9% sodium chloride after infusion is completed.

Example: For a 70kg patient

Total dose = 0.9mg/kg bodyweight

= 0.9 x 70 = 63mg alteplase

Bolus dose = 10% of total dose

= 0.1 x 63 = 6.3mg = 6.3mL⇒ give as IV push over 1 minute

Infusion dose = total dose minus bolus dose

= 63 - 6.3 = 56.7mg = 56.7mL, add to 50mL sodium chloride 0.9% minibag ⇒ infuse over 60 minutes.

Table 2 Dosing Table (based on reconstituted concentration of 1mg/mL of alteplase)

Weight (kg) **(approximate to nearest 5kg)**	**Total dose (mg) (dose = 0.9mg/kg)** **MAX DOSE: 90mg**	**Alteplase bolus dose volume (mL)** **(bolus = 10% of total)**	**Alteplase infusion dose volume (mL)** **(infusion = 90% of total)**	**Total infusion volume (mL) (approximate)**
100+	90.0	9.0	81.0	131
95	85.5	8.5	77.0	127
90	81.0	8.1	72.9	123
85	76.5	7.6	68.9	119
80	72.0	7.2	64.8	115
75	67.5	6.7	60.8	111
70	63.0	6.3	56.7	107
65	58.5	5.8	52.7	103
60	54.0	5.4	48.6	99
55	49.5	4.9	44.6	95
50	45.0	4.5	40.5	91
45	40.5	4.0	36.5	87
40	36.0	3.6	32.4	82
Patients > 55kg will require 50mg and 10mL vials.		**Bolus dose is given as an IV push over 1 minute.**	**Add to 50mL sodium chloride 0.9% minibag.**	**Infuse over 60 minutes until empty via volume control pump.**

Avoid thrombolytics, antiplatelet agents and anticoagulants for 24 hours post administration of alteplase.

Adverse reactions:

- Intracranial haemorrhage (see Appendix B for management)
- Gastrointestinal, genitourinary, retroperitoneal bleeding
- Nausea, vomiting
- Superficial bleeding from punctures or damaged blood vessels
- Anaphylactoid reactions
- Peri-oral and lingual angioedema (1 in 30 incidence up to 24 hours post infusion).

Compatibilities:

- Reconstitute with sterile water for injections without preservative only.
- Reconstituted solution may be further diluted up to 5 fold using 0.9% sodium chloride only. Do not use water for injections, glucose or preservative containing solutions for further dilutions.
- Do not mix alteplase with other drugs (including concurrent drug therapy in IV line).
- Patients on ACE inhibitors may have increased risk of suffering anaphylactoid reactions.

Product information: Actilyse® (alteplase), Boehringer Ingelheim.

7 Directions for care after thrombolysis

Protocol for post-alteplase care [3,7]

7.1 Guidelines for the early management of patients with ischaemic stroke

- Admit the patient to an ICU or stroke unit for monitoring. (Patients nursed in the stroke unit should have a nurse to patient ratio of 1:1 for the first 8 hours following alteplase administration.)
- Perform neurological assessments every 15 minutes during the alteplase infusion, every 30 minutes for the next 6 hours, and then hourly until 24 hours.
- Measure blood pressure every 15 minutes for the first 2 hours, every 30 minutes for the next 6 hours, and then every hour until 24 hours from treatment.
- If the patient develops severe headache, acute hypertension, nausea or vomiting, discontinue the infusion and obtain an urgent Cranial CT scan.
- Delay placement of nasogastric tubes (NGT), IDC (if not inserted prior to alteplase), or intra-arterial lines (see nursing considerations in the following section for further details).
- Increase the frequency of blood pressure measurements if a systolic blood pressure >180 mmHg or diastolic blood pressure of >105 mmHg is recorded.
- Administer antihypertensive medications to maintain blood pressure at or below these levels.
- If diastolic blood pressure 110mmHg or systolic blood pressure exceeds 180 mmHg, notify consultant on-call and follow unit protocols for post stroke hypertension. Commonly this involves commencement of intravenous glyceryl trinitrate (GTN) infusion, see Appendix A.
- If systolic still exceeds 180, or diastolic exceeds 105mmHg after 30 minutes consider transfer to an ICU for intravenous beta blockers or sodium nitroprusside.

7.2 Nursing considerations post alteplase administration

1. Monitor observations and blood pressure as per Appendix C.
2. Alteplase is compatible with sodium chloride 0.9%, ***not*** with glucose containing fluids or with fluids containing preservatives.
3. No bladder catheterisation within 90 minutes of completing alteplase.
4. Bladder management should be commenced and monitored closely. Catheterisation should be delayed if safe from the bladder point of view, for as long as possible after completion of the infusion. (See Appendix C.)

   The priority is for alteplase administration. Alteplase administration should not be delayed for catheterisation, NGT insertion or other procedures. If IDC is required, it should be placed by an experienced clinician. Use a small gauge. A bladder ultrasound may be helpful in decision making.
5. No punctures of arteries or large veins within 24 hours after starting alteplase.
6. Leave IV cannula insitu for blood collection. If emergency venopuncture is required, apply direct pressure to the site for 20 minutes.
7. Avoid NGT insertion until 8 hours post alteplase infusion.[8]

8. No antiplatelet therapy or anticoagulants within 24 hours after starting alteplase.
9. Commence BGL profile 8 hours post alteplase infusion.

Mobilisation should be carefully considered after alteplase as the patient is at risk of bleeding with falls or trauma.

The patient should be rest in bed for 12-24 hours post completion of alteplase (including toileting).

For an example of a nursing protocol post alteplase administration, refer to Appendix C.

- The patient will be monitored by a "Nurse Special" or suitable alternative for the first 24 hours.
- The patient is to be monitored in the high dependency area.
- Observations - full neurological observations (FNO) are to be performed post alteplase 1 at the following intervals:
  - Every 15 minutes for 2 hours
  - Every 30 minutes for 4 hours
  - Every 1 hour for 18 hours (unless otherwise directed by registrar).
- Report any neurological changes or evidence of haemorrhage to the Stroke Registrar/Consultant.
- Staff to use Stroke Care Plan and follow standard stroke protocols including:
  - Nutrition/dysphagia screen/Speech Pathology referral
  - Bladder/ bowel management
  - Mobility assessment/Physiotherapy referral
  - Braden Score – access correct mattress as required
  - Falls risk assessment
  - Mouth care/hygiene.

8 Counseling of patients and families

8.1 General information

There should be close involvement of the patient and the family in the decision to use interventional stroke treatments. Whilst formal consent is not required for IV alteplase, every effort possible should be made to contact the patient's next of kin or close family members in order to advise them of the risks and benefits of interventional therapy. Additionally, witnesses may be able to confirm the crucial time of onset and provide additional information about possible exclusion factors. The risks and benefits of alteplase must be discussed by the stroke team with the patient prior to treatment.

There are many ways of expressing the benefits and risks.

- Recombinant tissue plasminogen activator (tPA, or alteplase, or Actilyse®) administered intravenously has been shown to improve functional outcome in selected patients if given within 4.5 hours of onset of symptoms, despite an increased risk of intracranial haemorrhage.
- At 3 hours, about 8 patients need to be treated to make one more patient independent in activities of daily living three months after their stroke.
- At 3 hours, about 16 patients need to be treated to cause one more patient to suffer a bleed into the brain that causes them to deteriorate neurologically.
- The benefit is greater the earlier thrombolysis is given. I.e. although alteplase is approved up to 4.5 hours, the benefit diminishes between 3 and 4.5 hours.

Time to treatment is an important factor in defining outcome. This can be expressed as the number needed to treat (NNT) to achieve an excellent neurological outcome (defined as a Modified Rankin Score) at 3 months of 0 or 1, i.e. independence.

8.2 Time to treatment: number needed to treat (NNT) for significantly improved outcome*

< 90 minutes	3 patients
< 180 minutes	8 patients
< 279 minutes	14 patients

*Note: the NNT quoted already takes account of the small excess of haemorrhages listed above.

8.3 CT scan changes and thrombolysis

There is some controversy regarding the significance of CT scan changes, and how these may influence treatment decisions when using thrombolytic therapy. There are several key issues, including:

1. Duration of symptoms
2. Presence of overt parenchymal hypoattenuation
3. Presence of subtle early signs of ischaemia; i.e. loss of grey/white differentiation in the basal ganglia and insular cortex
4. Extent of subtle signs
5. Observer reliability in the identification of subtle signs.

A recent review of the NINDs data[9] suggested that the presence of subtle signs of ischaemia, even when exceeding one third of the MCA territory, did not predict intracranial haemorrhage in patients treated with IV alteplase within 3 hours.

The issue remains contentious and the Australasian Guidelines[10] reflect this.

The data from the European Cooperative Acute Stroke Study(ECASS) trials suggest that such changes exceeding one third of the MCA territory should be considered a contra-indication in the 3 to 6 hour time window.[11]

It should also be noted that overt hypoattenuation, when observed in the sub 3 hour time window, should prompt a reconsideration of the time of onset, and may be a contraindication to thrombolytic therapy.[12]

Conclusions

1. Overt hypoattenuation should caution against the use of alteplase and should prompt a re-evaluation of the time of onset.
2. Subtle signs of ischaemia (as defined above), even when exceeding one third of the MCA territory, may not contraindicate the use of alteplase, less than 3 hours after symptom onset.
3. Subtle signs of ischaemia exceeding one third of the MCA territory should contra-indicate the use of IV alteplase in the 3 to 6 hour time window.

Appendices

Appendix A: Management of blood pressure

Blood pressure (BP) may need to be controlled prior to alteplase administration or may develop during administration. Be cautious about dropping BP excessively or quickly.

Blood pressure monitoring during the first 24 hours post alteplase administration

Maintain BP < 180/110

The following regimen should be strictly adhered to:[3,7]

- 0 – 2 hours: every 15 minutes after initiation of infusion
- 2 – 6 hours: every 30 minutes after initiation of infusion
- 6 – 24 hours: every 60 minutes after initiation of infusion.

Monitoring blood pressure during treatment with glyceryl trinitrate (GTN)

During treatment with GTN infusion, blood pressure should be monitored every 15 minutes.

GTN must be administered via separate IV line as per your local hospital protocol. Note PVC containers and lines should be avoided.

Consider GTN if blood pressure on 2 readings (10 min apart) is:

1. Systolic BP >180 – 230 mmHg, or diastolic BP >110 – 120 mmHg

   → For example, GTN infusion 50 mg/100 ml, start at 3 ml/hour, titrate until BP <180/110 (6ml/hr = 50mcg/min).

   → After switching off, effect abates in minutes.

2. Consider IV metoprolol

3. Consider IV hydrallazine.

If BP is still high >180/110: Consider admission to HDA or ICU for treatment with IV sodium nitroprusside.

If a sudden rise in BP you should suspect an intracranial haemorrhage. Discontinue alteplase and get an urgent CT brain.

Appendix B: Management of intracranial haemorrhage

Suspect intracranial haemorrhage if:

1. Acute neurological deterioration
2. New headache
3. Nausea or vomiting
4. Acute increase in blood pressure.

If intracranial haemorrhage is suspected:

1. Discontinue alteplase administration
2. Organise CT brain
3. Bloods: FBC, APTT, INR, fibrinogen, cross match
4. Call haematology to provisionally request cryoprecipitate and platelets.

***If haemorrhage is observed**:*

1. Administration of cryoprecipitate 1 unit/10kg bodyweight.
2. If alteplase is still circulating at the time of the bleeding onset and immediate control of bleeding is required. Consider antifibrinolytic therapy (e.g. intravenous aminocaproic acid 0.1 g/kg over 30 minutes or aprotinin 2 million kallikrein inhibitory units over 30 minutes), while awaiting cryoprecipitate.
3. Consult neurosurgeon if indicated. The outlook is poor with or without surgery, occasionally salvage evacuation may have a limited role. Discuss with Neurosurgery on a case by case basis.
4. Recheck FBC, APTT, INR, fibrinogen after administration of cryoprecipitate and platelets, and target further administration of cryoprecipitate if fibrinogen levels remain less than 1.0 g/L, in consultation with haematologist.
5. Factor VIIa may have a controversial role. Consider if continues to deteriorate despite above measures and in discussion with Haematologist.

In case of bleeding elsewhere, cease alteplase and investigate and treat as clinically indicated. The principles regarding use of cryoprecipitate, platelets and antifibrinolytic therapy do not vary after administration of alteplase. In addition: call blood bank to arrange cross-match in case transfusion of fresh frozen plasma is required.

Consult Gastroenterologist, Haematologist, Neurosurgeon or Urologist as clinically indicated.

Appendix C: Management of peri-oral angioedema complicating alteplase treatment

- Peri-oral angioedema is an uncommon complication of alteplase treatment of acute ischaemic stroke, occurring in 1-5% of treated patients.
- It may occur during, or up to 2 hours after the infusion, and may be hemilingual, contralateral to the side of the stroke.
- Concurrent ACE inhibitor use and insular involvement of the stroke may be risk factors.
- The main differential diagnosis is a tongue haematoma.
- Management is empiric, based on expert opinion.

Suggested principles include:

1. Early anaesthetic consultation; intubation may be required for progressive airway obstruction. Tracheostomy must be avoided due to the thrombolytic effects of the alteplase.
2. IV hydrocortisone 100mg
3. IV promethazine 25mg (Must take care to avoid tissue extravasation and intra-arterial administration.)
4. IV ranitidine 50mg
5. Adrenaline should be avoided for fear of inducing hypertension.

Appendix D: Post alteplase administration - nursing protocol

<table>
<tr><td colspan="3">This document is to be used as a GUIDE ONLY.
Please ensure that you have referred to specific instructions from the Stroke Team managing the patient.
Recommendations are the minimum standard.
Instructions may vary from this guideline.</td></tr>
<tr><td colspan="3">PREPARATION OF THE WARD PRIOR TO ARRIVAL OF ALTEPLASE PATIENT</td></tr>
<tr><td>STAFFING</td><td colspan="2">The patient will require a 1:1 nurse special for 8 hours following the administration of alteplase. If the patient is neurologically unstable the nurse special may need to be continued. This will be reviewed by the suitably qualified nurse e.g. Clinical Nurse Specialist (CNS) or Neurology Nurse Practitioner.</td></tr>
<tr><td>BED SPACE</td><td colspan="2">The shift coordinator on receiving the stroke page will identify a bed on the ward and out lie if required to do so. They will liaise with the allocations manager about staffing levels for the next 8 hours. Check O_2 and suction are available.</td></tr>
<tr><td colspan="3">ADMISSION TO THE WARD</td></tr>
<tr><td>HANDOVER</td><td colspan="2">▪ Check medications given, the timing of administration and the patient’s response.
▪ Ensure medication charts and fluid prescription charts are signed Confirm that the neurological observations are the same in ED as they are on arrival to the ward.
▪ Report any discrepancies to the Stroke Registrar/consultant. Check BP parameters are charted.</td></tr>
<tr><td>OBSERVATIONS</td><td colspan="2">▪ Perform and document FNO as per the regimen below at a minimum.
▪ Every 15 minutes for 2 hours (2 hours total)
▪ Every 30 minutes for 4 hours (6 hours total)
▪ Every hour for 18 hours (24 hours total)
▪ Maintain the head of the bed at 30 degrees unless otherwise indicated.
▪ Head in neutral position.
▪ Commence Bladder Assessment.
▪ Check for blood in urine.
Immediately report any changes or deterioration in patient status to the Stroke Consultant</td></tr>
<tr><td></td><td>Monitor the patient for any signs of:</td><td>Time of symptom noted:</td></tr>
<tr><td></td><td>Intracranial haemorrhage / deterioration in Glascow Coma Scale (GCS)</td><td></td></tr>
<tr><td></td><td>Peri oral and lingual angioedema (1-30 incidence)</td><td></td></tr>
<tr><td></td><td>Nausea & vomiting</td><td></td></tr>
<tr><td></td><td>Anaphylactic reaction</td><td></td></tr>
<tr><td></td><td>Abdominal pain or distension</td><td></td></tr>
<tr><td></td><td>Fever</td><td></td></tr>
</table>

ON PATIENTS ARRIVAL TO THE WARD	
PRIORITIES	▪ Perform FNO and SaO_2 and document baseline. ▪ Connect O_2 at prescribed flow rate. ▪ Elevate the head of the bed to 30 degrees unless otherwise indicated. ▪ Head in neutral position. ▪ Bed rails insitu (consent required if utilised). ▪ Check blood results. ▪ Check patient for any signs of bleeding - IV sites, wounds, etc. Check for the last time the patient voided - begin bladder assessment. ▪ Inform next of kin of patients progress.
HYDRATION AND NUTRITION	▪ As per hospital Stroke Unit protocol. ▪ Maintain strict fluid balance chart. ▪ Ensure adequate IV hydration is available. ▪ Avoid NGT insertion until at least 8 hours post alteplase administration.[1,3] ▪ Arrange speech pathology review if indicated.
ELIMINATION	▪ Bladder management should be commenced immediately as per standard nursing practice. ▪ Monitor closely TBV and PVR if not catheterised prior to alteplase. ▪ Avoid IMC for at least 8 hours after alteplase infusion has ceased.[1,3] ▪ Avoid IDC for 24 hours after alteplase infusion has ceased if not sited prior to alteplase.[1,3] ▪ Monitor and chart all bowel actions.
MOBILITY AND HYGIENE	▪ TED stockings. ▪ Falls risk assessment prior to mobilisation. ▪ Mobilise as per ward protocol. ▪ Wash in bed, regular mouth and eye care. ▪ No razor blade for shaving. ▪ Braden score - pressure relieving mattress and regular pressure care.
SPECIAL PRECAUTIONS	▪ Minimise physical handling of the patient. ▪ Minimise invasive procedures during the first 8 hours post alteplase. ▪ Leave IV cannula in for blood collection. ▪ If venopuncture is required, apply direct pressure to the site for 20 minutes. ▪ Commence BSL profile 24 hours after alteplase.
AFTER 8 HOURS CONTINUE WITH USUAL STROKE UNIT PROTOCOL	

Appendix E: Frequently asked questions

Q. What is the benefit of treatment with alteplase within 3 and within 6 hours of onset of symptoms?

A. When treating with alteplase, within 3 hours, there will be 110 (95% CI 50 to 170) more independent survivors per 1000 patients treated; treatment within 6 hours results in 40 (95% CI 10 to 80) more independent survivors per 1000 patients treated.[3]

Or expressed in odd ratios (OR):

Alteplase within 3 hours reduces the risk of death and dependency by an odds of 36% (OR 0.64, 95% CI 0.50 to 0.83, based on 5 trials including a total of 930 patients).[3]

Alteplase within 6 hours reduces the risk of death and dependency by an odds of 20% (OR 0.8, 95% CI 0.69 to 0.93, based on 6 trials including a total of 2830 patients); this includes the significant adverse effect on death within the first 10 days (OR 1.24, 95% CI 0.85 to 1.81).[3]

Q. What is the risk of symptomatic (including fatal) intracranial haemorrhage within 7-10 days?

A. Symptomatic haemorrhage (including fatal): Fourfold increase in risk compared to placebo: 10% compared to 3% (OR 3.1, 95% CI 2.3 to 4.0). [3]

Fatal haemorrhage: 4% (t-PA) compared to 1% (placebo) (OR 3.6, 95% CI 2.3 - 5.7). [7]

Q. Is there still a net benefit in the 4.5-6 hours time-window?

A. Unclear, IST-3 investigates this. Systematic review of the current data on alteplase suggests that there may be, reducing the odds of death and dependency by about one quarter (OR 0.76, 95% CI 0.60 to 0.96).[14]

Q. What should be done if there are early signs of ischaemic stroke on the CT scan?

A. The relative importance of these signs is still unclear. There is possibly a higher risk of intracranial haemorrhage, but it is unclear whether this is offset by excess of deaths from cerebral oedema and transtentorial herniation in not treated patients. → Randomise IST-3.

Q. Is a patient with a severe lacunar syndrome eligible?

A. Yes, the positive effect of alteplase was shown to be consistent in patients with presumed small-vessel occlusive disease, large-vessel occlusive disease, and cardio-embolic ischaemic stroke. [14]

Q. Is a patient with an ischaemic stroke of the brainstem eligible?

A. There is currently no controlled data available. Consider randomisation in IST-3 or empirical treatment with intra-arterial thrombolysis.

Q. Is a patient with a cerebellar infarct eligible, taking into account potentially very serious effect of infratentorial haemorrhage?

A. There is currently no data available, consider randomising in IST-3.

Appendix F: Examples of site specific hospital rapid response protocols

SCGH: THE ACUTE STROKE TEAM AND CODE STROKE PAGER

The acute stroke team is designed to provide a rapid response for stroke patients by a team of experts in acute stroke assessment. The team is activated by a group pager, usually at the discretion of the Neurology Registrar who dials “55” and states; “stroke team to attend…desired location (usually ED or the CT Suite)”.

The following personnel will be notified during normal working hours (0900 to 1700).

1. The Stroke Unit Neurologist will have sole overall clinical responsibility for the management of the patient.
2. On call Interventional Neuroradiology Fellow; meets the stroke team in the CT Suite and assists with the interpretation of the CT, CT angiogram (CTA), and assists with arrangements for interventional cerebral angiography if necessary.
3. The Stroke Clinical Nurse Consultant (CNC) assists with overall running of the code stroke, particularly to make arrangements for admission to G51or other appropriate destination. Additionally she will help to locate the patient’s family to commence counselling regarding interventional therapy and during working hours bring the “alteplase kit” to the code.
4. Ward G51 Clinical Nurse Specialist; work with nursing management to arrange bed on G51 and a “nurse special”.
5. Ward G51 Clinical Nurse Co-ordinator of the day; commences arrangements to make a bed on G66 liaises with the ED shift co-ordinator, and after hours arranges for alteplase to be sent to ED via chute.
6. Remaining Neurology Registrars: assist the Neurology Registrar covering ED by gathering laboratory results and by covering other calls and patients whilst the code stroke is active.
7. Outside normal working hours, team members 2 and 5 are activated by the group pager.

The team will meet within a week of all code strokes to review all aspects of the code, to particularly identify areas of delay. This should include all patients, regardless of whether interventional therapy was administered.

ROYAL PERTH HOSPITAL

Royal Perth Hospital Stroke Team and Group Page Number 2828.

A rapid coordinated response is required for all stroke patients presenting in the ED within 4 hours of onset of symptoms.

The Royal Perth Stroke Team is contactable on Group **Page 2828** from 0830 – 1530 hours in the event of a patient who is a possible candidate for thrombolysis.

This is activated by the ED Team.

The Attending Stroke Team consists of:

- Stroke Registrar
- Stroke Resident
- Stroke Liaison Nurse
- Neurology Registrars on duty.

They attend the ED taking with them the IST-3 drugs and kit. A full neurological examination is done normally whilst waiting for CT.

The Attending Stroke Team liaises with the ED staff, the patient and their family member/s if available.

Once there is a diagnosis of an ischemic event the following steps should be taken.

1. The Senior Neurologist is contacted to consult on initial clinical management of the patient.
2. If recommendation for intervention is made by the Attending Stroke Team the patient's family is consulted and counselled with reference to possible outcomes.
3. If IST-3 is to be used (3 – 6 hours post event) the resident assembles all documentation to submit the patient for randomisation and telephones the Trial Centre as per protocol.
4. The CNS of Ward 8A is notified to facilitate admission to the Ward in the High Dependency Area and arrange for a "nurse special" or other suitable staffing to monitor the patient for the first 24 hours.
5. Stroke Liaison Nurse assists as required with family consultation and access. Assist the team and monitor the patient in the ED until transferred to Ward 8A.
6. Neurology Registrars on duty assist in ED as required or cover the ward in the Stroke Registrars absence.
7. Outside normal hours and weekends the on duty Neurologist is consulted by ED staff.
8. The Clinical Nurse Coordinator of ward 8A are notified directly to arrange a bed.

Appendix G: Acronyms (alteplase guidelines)

ABCs – Airways, Breathing, Circulation

ACE – Angiotensin-Converting Enzyme

APTT – Activated Prothrombin Time

BSL – Blood Sugar Level

CNS – Clinical Nurse Specialist

COAGS – Coagulation Screen

CT – Computerized Tomography

CT – Computerized Tomography Angiogram

CXR – Chest X ray

ECASS – European Cooperative Acute Stroke Study

ECG – Electrocardiogram

ED – Emergency Department

FBC – Full Blood Count

FNO – Full Neurological Observations

GCS – Glascow Coma Scale

GTN – Glyceryl Trinitrate

HDA –High Dependency Area

ICU – Intensive Care Unit

INR – International Normalised Ratio

IV – Intravenous

IST-3 – International Stroke Trial 3

MCA – Middle Cerebral Artery

NGT – Nasogastric Tubes

NIHSS – National Institutes of Health Stroke Scale

NIISWA – Neurological Intervention and Imaging Service of Western Australia

NINDs – National Institute of Neurological Diseases and Stroke

RPH – Royal Perth Hospital

SCGH – Sir Charles Gairdner Hospital

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