The results comparing Activase- and 50 mg Vial 74972.qxp 2/1/2006 1:31 PM Page 1

1). The results comparing Activase- and 50 mg Vial 74972.qxp 2/1/2006 1:31 PM Page 1

1.30–4.00 mmol/L in an international, multicenter trial (GUSTO). Both treatment groups were started in the absence of fibrin. When introduced into the systemic circulation at pharmacologic concentration, Activase binds to a fibrinogen and converts the activated plasminogen to plasmin. This initial local fibrinolysis with systemic fibrinolysis has been confirmed in patients experiencing acute myocardial infarction. In a controlled trial, 8 of 73 patients (11%) receiving Activase (1.25 mg/kg body weight) for 1 hour or 3 hours experienced a death or a fibrinogen level below 100 ng/mL. The benefit of fibrinolysis is conferred on the patient with an initial platelet half-life of less than 5 minutes. There is no difference in the dominant initial platelet half-life between the IV and accelerated regimens for AA. The plasma clearance of Activase is 0.30–0.50 mL/min.) The clearance is mediated primarily by the liver. The initial volume of distribution approximates plasma volume.

Table 1 presents 90-minute, 180-minute, 24-hour, and 5–7 day patency values by TIMI grade for patients treated with placebo and Activase.

The exact relationship between coronary artery patency and clinical activity has not been established.

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Table 2  The MINDS 1-PA Stroke Trial, Part 2

3-Month Efficacy Outcomes

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo (n=372)</th>
<th>Activase (n=372)</th>
<th>Difference*</th>
<th>Frequency*</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable Outcome†</td>
<td>193 (52.2%)</td>
<td>205 (55.1%)</td>
<td>12%</td>
<td>55%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

†Favourable Outcome defined as recovery of minimal or no disability.

Placebo vs. Activase

Table 4  The MINDS 1-PA Stroke Trial

SAFETY OUTCOMES

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Placebo (n=372)</th>
<th>Activase (n=372)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (5.4%)</td>
<td>16 (4.3%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>16 (5.1%)</td>
<td>16 (4.3%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Symptomatic ICH within 36 hours</td>
<td>2 (0.6%)</td>
<td>2 (0.6%)</td>
<td>0.36</td>
</tr>
<tr>
<td>New Ischaemic Strokes (3-months)</td>
<td>17 (4.6%)</td>
<td>18 (4.8%)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Table 3  The MINDS 1-PA Stroke Trial

INDICATIONS AND USAGE

Acute Myocardial Infarction

Use in Acute Myocardial Infarction

Before the use of thrombolytic agents in the management of acute myocardial infarction in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure, and the reduction of mortality associated with AMI. Treatment should only be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY).

The diagnosis should be confirmed by objective means, such as pulmonary angiography or other diagnostic imaging methods for the presence of hemodynamics (see CONTRAINDICATIONS).

Pulmonary Embolism

Treatment of ICH

Following the diagnosis of intracerebral hemorrhage by a neuroradiologist or another physician designated by the clinician (see CONTRAINDICATIONS).

A recent intracerebral or intracranial surgery, serious head trauma, or previous stroke

History of intracranial hemorrhage

Uncontrolled hypertension at time of treatment (e.g., > 180 mm Hg systolic or > 110 mm Hg diastolic)

Tolerance of the need of stroke

Asymptomatic ICH

Intracerebral, intracerebral hemorrhage or intracranial surgery

Recent intracerebral hemorrhage or intracranial surgery evaluation

Presence of intracranial hemorrhage or intracranial surgery evaluation

Recent (within 2 months) intracerebral or intracranial surgery, serious head trauma, or previous stroke

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**ACTIVASE® (Alteplase)**

In acute ischemic stroke, whether the incidence of intracranial hemorrhage nor the benefits or risks of treatment are increased with the accelerated infusion regimen compared with the 3-hour regimen. Therefore, treatment of patients with acute ischemic stroke more than 3 hours after symptom onset is not recommended.

Due to the increased risk for intracranial hemorrhage of acute ischemic stroke, special diligence is required in making diagnoses in patients whose glucose values are < 70 mg/dL (< 4 mmol/L), or > 400 mg/dL (> 22 mmol/L). The safety and efficacy of treatment with Activase in patients with minor neurological deficit or with rapidly improving symptoms is not recommended.

**PRECAUTIONS**

General

Management of myocardial infarction or pulmonary embolism should be implemented concurrently with Activase treatment. Noncomparable anticoagulants must be avoided in postinfusion therapy. Any serious bleeding should be stopped immediately, along with any anticoagulants being administered. Repairable effects can be reversed by platelets.

Anticoagulants

The concomitant use of heparin or aspirin during the first 24 hours following symptom onset in patients treated with Activase for the management of acute ischemic stroke is unknown. (see PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Active Anticoagulants). Onset of anticoagulation in patients who receive Activase more than 12 hours after onset of acute ischemic stroke in patients receiving concomitant Angiotensin-converting enzyme inhibitors. Patients treated with Activase should be monitored during and for several hours after infusion for signs of aortic dissection or intimal injury, occurrence of other bleeding complications (e.g., peptic ulceration, gastrointestinal, retroperitoneal or gastrointestinal) occur, Activase therapy should be discontinued immediately, along with any anticoagulants being administered. Repairable effects can be reversed by platelets.

Bleeding

Use of Antithrombotics

The interaction of Activase with other cardioactive and cerebroactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole and Abciximab) may increase the risk of bleeding if administered prior to, during, or after Activase therapy. Activase contains low levels of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150–200 units/mL) can to some extent mitigate this phenomenon. (see PRECAUTIONS: Antithrombotics). A study of another alteplase product, Actilyse, in acute ischemic stroke patients receiving the 9-hour infusion regimen. The incidence of ICH, especially symptomatic ICH, in patients with acute ischemic stroke was 1.2% (3/250 patients) compared with 0.5% (1/200 patients) in placebo treated patients receiving the 3-hour infusion regimen. There have been post-marketing reports of orolingual angioedema associated with the use of Activase. Many patients, primarily acute ischemic stroke patients, were receiving concomitant Anticoagulation-converting enzyme inhibitors. Activase patients with Activase should be monitored during and for several hours after infusion for signs of upper airway hemorrhage from intubation trauma. Activase administration in the management of acute ischemic stroke. In The NINDS t-PA 3-3, patients were receiving concomitant Angiotensin-converting enzyme inhibitors. Patients treated with Activase should be monitored during and for several hours after infusion for signs of aortic dissection or intimal injury, occurrence of other bleeding complications (e.g., peptic ulceration, gastrointestinal, retroperitoneal or gastrointestinal) occur, Activase therapy should be discontinued immediately, along with any anticoagulants being administered. Repairable effects can be reversed by platelets.

Adverse effects from Activase therapy are similar to those that have been documented with other fibrinolytic agents. Readministration of Activase has not been conducted in patients who have previously received the drug, and the safety of this practice is unknown.

Drug Interactions

During Activase therapy, if coagulation tests and/or measures of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent in vitro artifacts. Activase is an enzyme that when present in blood in pharmacologic concentrations can cause fibrinogen degradation. This can lead to depression of fibrinogen levels and false positive results in tests for coagulation activity. Therefore, the interpretation of these tests in the presence of Activase is difficult and should be performed with caution. Patients treated with Activase and heparin should be closely monitored during the first 24 hours following symptom onset for signs of upper airway hemorrhage from intubation trauma. Activase contains low levels of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150–200 units/mL) can to some extent mitigate this phenomenon.

**ADVERSE REACTIONS**

Allergic Reactions

The incidence of intracranial hemorrhage (ICH) in acute myocardial infarction patients treated with Activase is as follows:

<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of Patients</th>
<th>ICH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg</td>
<td>3,271</td>
<td>1.1</td>
</tr>
<tr>
<td>100 mg accelerated</td>
<td>1,556</td>
<td>0.7</td>
</tr>
<tr>
<td>100 mg</td>
<td>1,579</td>
<td>1.3</td>
</tr>
<tr>
<td>1.0-1.4 mg/kg</td>
<td>237</td>
<td>0.4</td>
</tr>
</tbody>
</table>

These data indicate that a dose of 150 mg of Activase should not be used in the treatment of AMI because it has been associated with an increase in intracranial bleeding.

For acute pulmonary embolism, bleeding events were consistent with the general safety profile observed with Activase in acute myocardial infarction patients receiving the 3-hour infusion regimen. The incidence of ICH, especially symptomatic ICH, in patients with acute ischemic stroke was 1.2% (3/250 patients) compared with 0.5% (1/200 patients) in placebo treated patients receiving the 3-hour infusion regimen. There have been post-marketing reports of orolingual angioedema associated with the use of Activase. Many patients, primarily acute ischemic stroke patients, were receiving concomitant Anticoagulation-converting enzyme inhibitors. Activase patients with Activase should be monitored during and for several hours after infusion for signs of upper airway hemorrhage from intubation trauma. Activase contains low levels of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150–200 units/mL) can to some extent mitigate this phenomenon.

**Nursing Mothers**

There is no experience with readministration of Activase. If an anaphylactic-type reaction occurs, the patient should be treated immediately and appropriately. Activase contains low levels of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150–200 units/mL) can to some extent mitigate this phenomenon.

**General**

Nursing Mothers

There is no experience with readministration of Activase. If an anaphylactic-type reaction occurs, the patient should be treated immediately and appropriately. Activase contains low levels of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150–200 units/mL) can to some extent mitigate this phenomenon.
ACTIVASE® (Alteplase)

a. The bolus dose may be prepared in one of the following ways:
   1. By removing 6 to 10 mL from a port (second injection site) on the infusion line after
      the Activase vial from the plastic molded capping attached to the bottom of the vial.

b. The remainder of the Activase dose may be administered as follows:
   1. By removing 15 mL from the vial of reconstituted (1 mg/mL) Activase using a syringe
      and needle. If this method is used with the 50 mg vial, the syringe should be used for
      each patient treatment. Insert the spike end of an infusion set through the same puncture site
      made by the transfer device in the stopper of the vial of reconstituted Activase. Hang
      the Activase vial from the plastic molded capping attached to the bottom of the vial.
   2. By removing 6 to 10 mL from the vial of reconstituted (1 mg/mL) Activase using a syringe
      and needle. If this method is used with the 50 mg vial, the syringe should be used for
      each patient treatment. Insert the spike end of an infusion set through the same puncture site
      made by the transfer device in the stopper of the vial of reconstituted Activase. Hang
      the Activase vial from the plastic molded capping attached to the bottom of the vial.
   3. By programming an infusion pump to deliver the appropriate volume as a bolus at
      the infusion rate of the Activase vial.
   4. By removing the protective cap from one end of the transfer device and keeping the vial of SWFI
      (100 mL Sterile Water for Injection, USP) inverted. Insert the spike end of an infusion set
      through the same puncture site created by the transfer device in the stopper of the vial of reconstituted
      Activase. Hang the vial of SWFI upside-down, position it so that the center of the stopper is
      directly opposite the second injection site, place the vial of SWFI near the patient, and
      begin the infusion. Do not use beyond the expiration date stamped on the vial.

Storage: Store Hypoactive Alteplase at controlled room temperature not to exceed 30°C (86°F), in
sterile conditions, in containers suitable for their intended use, for up to 6 months from the date of
manufacture. After opening the container, Alteplase should be used immediately or refrigerated
undisturbed for several minutes is usually sufficient to allow dissipation of any large bubbles.

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ACTIVASE® (Alteplase)

100 mg Vial

1. Reconstitute with the recommended volume of sterile water. Do not use other infusion solutions, e.g.,
   Sterile Water for Injection, USP, or preservative-free saline, as the diluent. Alteplase has no effect on
   the stability of these solutions. Excessive agitation during dilution should be avoided. Particulate matter
   and discoloration prior to administration whenever solution and container permit.

2. By removing 15 mL from a port (second injection site) on the infusion line after
   the Activase vial from the plastic molded capping attached to the bottom of the vial.

3. By programming an infusion pump to deliver a 15 mg aliquot 15 minutes with 10% of the total dose administered as an initial intravenous bolus over 1
   minute. Follow with 10% of the total dose over the next 15 minutes. The recommended dose is
   0.9 mg/kg (not to exceed 90 mg total dose) infused over 60 minutes with 10% of the total dose administered as an initial intravenous bolus over 1
   minute. Follow with 10% of the total dose over the next 15 minutes. The recommended dose is
   100 mg administered in the first hour at a rate of 1 mg/kg/hour without exceeding 10 mg/kg/hour. For smaller patients (< 20 kg), a dose of 1.25 mg/kg administered over 3 hours, then 0.625 mg/kg administered over 3 hours,
   has no effect on the stability of these solutions. Excessive agitation during dilution should
   be avoided. Particulate matter and discoloration prior to administration whenever solution and container permit.

DO NOT USE IF VACUUM IS NOT PRESENT.

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