Alteplase (Cathflo™ Activase®)

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Drug name: Alteplase, marketed as Cathflo™ Activase® (Genentech, Inc., South San Francisco, CA), is a human tissue plasminogen activator (t-PA) produced by recombinant DNA technology.

Classification: Thrombolytic

Action: As with native t-PA, alteplase is highly fibrin specific and thus acts specifically on fibrin-rich clots in catheter occlusion. Alteplase works by targeting fibrin (the substance that causes blood to clot), dissolving the thrombus (blood clot) and restoring function to the central venous access device (CVAD).

Indications: Alteplase is indicated for the restoration of function to CVADs as assessed by the ability to withdraw blood (Genentech, Inc., 2002).

Efficacy: U.S. Food and Drug Administration approval for alteplase is based on two phase III clinical trials designed to assess safety and efficacy. A placebo-controlled, double-blind, randomized trial (Cardiovascular Thrombolytic to Open Occluded Lines [COOL]) Efficacy Trial and a larger, open-label trial (COOL-2) investigated the use of alteplase in patients who had an indwelling CVAD for administration of chemotherapy, total parenteral nutrition, or long-term administration of antibiotics or other medications (Genentech, Inc., 2002).

Both studies enrolled patients whose catheters were not functioning (defined as the inability to withdraw at least 3 cc of blood from the device) but with the ability to instill the necessary volume of study drug. Restoration of function was assessed by successful withdrawal of 3 cc of blood and infusion of 5 cc of saline through the catheter. Patients with known mechanical occlusion as well as patients who were younger than two years old or weighed less than 10 kg were excluded from both studies (Deitcher et al., 2002; Ponec et al., 2001). Alteplase restored function in 67% of catheters with one 2 mg/2 ml dose and in 88% of catheters with up to 2 mg/2 ml doses (Deitcher et al.; Genentech, Inc., 2002; Ponec et al.).

Metabolism: Alteplase limits systemic exposure because it dwells in the catheter in direct exposure to the clot. Although a small amount may enter the bloodstream, circulating plasma levels are not expected to reach pharmacologic concentrations because of the drug’s short half-life.

If a 2 mg dose (recommended for patients weighing 30 kg or more) of alteplase was administered by bolus injection directly into the systemic circulation (rather than instilled into the catheter), the concentration of circulating alteplase would be expected to return to endogenous circulation levels of 5–10 ng/ml within 30 minutes. Clearance is mediated primarily by the liver (Genentech, Inc., 2002).

Half-life: The initial half-life of alteplase is less than five minutes when in circulation.

Adverse events: Few serious adverse events were reported in the COOL-2 trial, the largest published study of the use of thrombolytics for restoring function to occluded CVADs (N = 995). Patients received a 2–4 mg cumulative dose of alteplase. The most serious adverse events reported in clinical trials were sepsis, gastrointestinal bleeding, and venous thrombosis (Genentech, Inc., 2002). Adverse events in the COOL-2 trial included sepsis (0.4%), major hemorrhage (defined as a severe blood loss, blood loss requiring transfusion, or blood loss causing hypotension) (0.4%), gastrointestinal bleeding (0.3%), and venous thrombosis (0.3%). Intracranial hemorrhages or embolic events were not reported (Deitcher et al., 2002; Genentech, Inc.).

Dosage: Alteplase is instilled into the catheter at a concentration of 1 mg/ml. The recommended dosage for patients weighing 30 kg or more is 2 mg/2 ml; for patients weighing 10 kg or more but less than 30 kg, the dosage is 110% of the internal lumen volume of the catheter, not to exceed 2 mg/2 ml. If catheter function is not restored at 120 minutes after one dose of alteplase, a second dose may be instilled. Information on the efficacy or safety of dosing in excess of 2 mg per dose for this indication is not available (Genentech, Inc., 2002).

Dilution and reconstitution: Alteplase is a sterile, white to pale yellow lyophilized powder and should be reconstituted immediately before use.

Administration: Reconstitute alteplase to a final concentration of 1 mg/ml.

Preparation of solution
1. Withdraw 2.2 ml of sterile water for injection, USP. Diluent is not included. Do not use bacteriostatic water for injection, USP.
2. Inject the 2.2 ml of sterile water for injection, USP, into the alteplase vial, directing the stream into the powder. If slight foaming occurs, let the vial stand undisturbed to allow large bubbles to dissipate.

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Alteplase (Cathflo™ Activase®) Patient Instruction Sheet

Action: Alteplase is a medication that your nurse puts into your catheter to dissolve a blockage. It works by activating a substance in your blood that breaks down the blood clot, restoring function to most catheters. Alteplase also may be used to help keep your catheter functioning, so you may not need to have it replaced. For a small percentage of patients, however, alteplase may not be able to resolve the blockage.

How is the drug given? Your nurse will put the alteplase directly into your catheter. It may work in as few as 30 minutes or as long as four hours.

Why am I receiving this drug? Catheters frequently become occluded, which means that something is blocking the tube that has been inserted into your body. A blood clot may be occluding (or blocking) your catheter (also known as a central venous access device [CVAD]). This blockage makes it difficult or impossible to withdraw blood or for you to receive medical treatments. Several different things can cause CVAD occlusions, but the most common cause is thrombus (a blood clot) in the tube or around its tip. The U.S. Food and Drug Administration has approved alteplase as a clot dissolver used to restore function to CVADs.

Side effects: Alteplase has been proven to be safe. In studies to test alteplase, the most serious problems reported after injection were infection in the blood (0.4% of patients), bleeding in the stomach or intestines (0.3% of patients), and blood clots in the veins (0.3% of patients).

Precautions: If you have an allergy to alteplase (recombinant) or alteplase, notify your nurse or other healthcare professional.

What should I report to the physician or nurse? If you notice anything unusual about the way you feel after alteplase has been administered, notify your nurse immediately.

3. Mix by gently swirling until the contents are completely dissolved. Do not shake. Reconstituted solution should be colorless or pale yellow and transparent containing 1 mg/ml of alteplase.

4. Alteplase contains no antibacterial preservatives and should be reconstituted immediately before use. The solution may be used for intracatheter instillation within eight hours following reconstitution when stored at 2°–30°C (36°–86°F).

5. No other medication should be added to solutions containing alteplase.

Instillation of solution into the catheter

6. Withdraw 2 ml (2 mg) of reconstituted solution from the vial.

7. Instill the appropriate dose of alteplase into the catheter.

8. Dwell for 30 minutes. Assess catheter function by attempting to aspirate blood. If the catheter is functional, go to step 10. If not, go to step 9.

9. Assess catheter function after 120 minutes of dwell time by attempting to aspirate blood. If the catheter is still occluded, a second dose may be instilled. Repeat steps 1–8.

10. Aspirate 4–5 ml of blood if function has been restored. Aspirating removes alteplase and the residual clot. Gently irrigate the catheter with 0.9% sodium chloride, USP.

11. Discard any unused solution.

Availability: Alteplase is individually packaged as a sterile lyophilized powder in 2 mg vials.

Stability and storage:
- Store lyophilized alteplase at a refrigerated temperature (2°–8°C/36°–46°F).
- Do not use alteplase beyond the expiration date on the vial.
- Protect the lyophilized material from excessive exposure to light during storage.
- Once reconstituted, the solution may be used within eight hours if stored at 2°–30°C (36°–86°F).

Interactions: The interaction of alteplase with other drugs and concomitant use of drugs affecting coagulation or platelet function have not been formally studied. Therefore, no other medication should be added to solutions containing alteplase.

Contraindications: Alteplase should not be administered to patients with known hypersensitivity to the drug or any component of the formulation.

Warnings: None

Precautions: General:
- Catheter dysfunction may be caused by a variety of conditions other than thrombus formation, such as catheter malposition, mechanical failure, constriction by a suture and lipid deposits, or drug precipitates within the catheter. These types of conditions should be considered before treatment with alteplase.
- Because of the risk of damage of the vascular wall or collapse of soft-walled catheters, vigorous suction should not be applied during attempts to determine catheter occlusion.
- Excessive pressure should be avoided when alteplase is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the systemic circulation.

Bleeding: The most frequent adverse reaction associated with thrombolytics in all approved indications is bleeding. Alteplase has not been studied in patients known to be at risk for bleeding events that may be associated with the use of thrombolytics. Caution should be exercised with patients who have active internal bleeding or who have had any of the following within 48 hours: surgery, obstetrical delivery, percutaneous biopsy of viscera or deep tissues, or puncture of noncompressible vessels. In addition, caution should be exercised with patients who have thrombocytopenia, other hemostatic defects, or any condition for which bleeding constitutes a significant hazard or would be particularly difficult to manage, as well as those who are at high risk for embolic complications.

Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with alteplase should be stopped and the drug should be withdrawn from the catheter.

Infections: Alteplase should be used with caution in the presence of known or suspected infections in the catheter. Using alteplase in patients with infected catheters may release a localized infection into the systemic circulation.

Readministration: In clinical trials, patients received up to two 2 mg/2 ml doses (4 mg total) of alteplase. Additional readministration of alteplase has not been studied.

Use during pregnancy or in nursing mothers: No adequate and well-controlled studies in pregnant women have been conducted. Whether alteplase is excreted in human milk is unknown.

Pediatric use: Alteplase has not been studied in patients younger than two years or who weigh less than 10 kg. In clinical trial, 126 (11%) of 1,135 patients treated were from 2–16 years of age. No drug-related adverse events were observed in these patients. However, enrollment was insufficient to draw conclusions regarding the relative efficacy in the pediatric or low-weight subgroups, relative efficacy related to catheter types used in these patients, or relative rates of adverse events (Deitcher et al., 2002; Ponec et al., 2001).

(Continued on page 420)
**Nursing implications:**
- Because CVADs are critical for delivering life-saving IV therapies and allowing for the withdrawal of blood samples, their patency must be maintained (Wingerter, 2003). Catheter occlusions are responsible for an estimated 25%–70% of CVAD complications, of which the majority is thrombotic (Wingerter).
- Patients at the highest risk for thrombosis are those who experience venous stasis, enhanced blood coagulability, or trauma to the vessel wall—conditions not uncommon among patients requiring central venous access (Genentech, Inc., 2002). Certain catheter characteristics, such as left-sided placement or those with larger diameters, are more susceptible to thrombosis. The risk is also higher with polyvinylchloride and polyethylene catheters relative to the newer polyurethane and silicone CVCs.

**Patient education:** Nurses administering alteplase to patients should do the following.
- Educate patients regarding the purpose of the drug, its mechanism of action, and how it is administered.
- Inform patients that alteplase may remain in the catheter for up to two hours and that a second dose may be required.
- Inform patients that alteplase has been proven to be safe and no serious adverse reactions have been reported with the use of this drug during clinical trials.

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