This reprint contains data from a Genentech-sponsored phase III clinical trial that led to the approval of Genentech's product Cathflo® Activase® (alteplase) for pediatric patients. The FDA has approved Cathflo® Activase® (alteplase) for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

This reprint contains information that is not contained in the approved product labeling, including special considerations of maintaining CVADs in pediatric patients; history of catheter thrombolysis; rationale for the CAPS trial; additional information on materials, methods, and patients of the CAPS trial; and limitations of the CAPS trial.

The following author(s) of the attached publication are present or former employees of Genentech: Martha Blaney, Sarah Gray, Jennifer Armfield, and Charles P. Semba.

Important Safety Information for Cathflo® Activase® (alteplase)

Contraindications
Cathflo Activase should not be administered to patients with known hypersensitivity to alteplase or any component of the formulation.

Precautions

General
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen). These types of conditions should be considered before treatment with Cathflo Activase.

Excessive pressure should be avoided when Cathflo Activase is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation.

Bleeding
The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Cathflo Activase 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 any condition for which bleeding constitutes a significant hazard.

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retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

Infections
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation. As with all catheterization procedures, care should be used to maintain aseptic technique.

Hypersensitivity
Hypersensitivity, including urticaria, angioedema and anaphylaxis, has been reported in association with use of Cathflo Activase. Monitor patients treated with Cathflo Activase for signs of hypersensitivity and treat appropriately if necessary.

Drug Interactions and Drug/Laboratory Test Interactions
The interaction of Cathflo Activase with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied.

Potential interactions between Cathflo Activase and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Cathflo Activase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions
In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see accompanying full Prescribing Information for additional important safety information.

Alteplase for the Treatment of Central Venous Catheter Occlusion in Children: Results of a Prospective, Open-label, Single-arm Study (The Cathflo Activase Pediatric Study)

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PURPOSE: Alteplase is approved for use in the restoration of function to occluded central venous access devices (CVADs); however, there are few prospective studies in children. This study was undertaken to evaluate the safety and efficacy of alteplase in the treatment of CVAD occlusions in a pediatric population.

MATERIALS AND METHODS: A prospective, multicenter, open-label, single-arm study evaluating a maximum of two doses (≤2 mg per dose) of alteplase was performed in pediatric patients. Inclusion criteria included patient age less than 17 years with an occluded CVAD (single-, double-, and triple-lumen catheter or implanted port). Patients with hemodialysis catheters, those with known mechanical occlusion, or those considered at high risk for bleeding or embolization were excluded. Assessment of function was made 30 and 120 minutes (if required) after each dose. The primary objective of the study was to evaluate the safety of alteplase as measured by the incidence of intracranial hemorrhage (ICH); secondary objectives included the evaluation of specific targeted serious adverse events and efficacy of alteplase in the restoration of catheter function.

RESULTS: A total of 310 patients (174 male patients, 136 female patients; mean age, 7.2 years; range, 0.04–18.3 y) were treated; 55 of the patients (17.7%) were younger than 2 years of age. No patients experienced ICH (95% CI, 0%–1.2%). Nine serious adverse events were noted in eight patients (2.6% incidence), two of which were attributed by the investigator to study drug administration (one case of sepsis and one case of a ruptured catheter lumen). The cumulative rate of restoration of CVAD function after serial administration of a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes, was 82.9% (95% CI, 78.2%–86.9%). Similar rates of catheter function restoration were seen among all catheter types studied; there were no clinically meaningful differences among age or sex subgroups.

CONCLUSION: The administration of alteplase is safe and effective for the restoration of function to CVADs in pediatric patients.

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Abbreviations: CAPS = Cathflo Activase Pediatric Study, COOL = Cardiovascular Thrombolytic to Open Occluded Lines [trial], CVAD = central venous access device, FDA = Food and Drug Administration, ICH = intracranial hemorrhage

THE preservation of central venous access devices (CVADs) in children remains a challenging medical management dilemma (1). CVAD care is distinctly different in children from that in adults; children tend to have fewer veins to select from, and the catheters have smaller bores with significantly smaller lumen volumes than do the catheters used in adults. Placement of the access devices often requires cooperative input from pediatricians/neonatologists, anesthesiologists, surgeons, interventionalists, nurses, and parents. Replacement or exchange of an occluded CVAD in a sick child can be a vexing issue resulting in interrup-

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tion of therapy, need for scheduled room time (operating room or angiography suite), repeat operative intervention, use of general anesthesia, and incremental health care costs to deal with delays and additional procedures. Therefore, the ability to noninvasively salvage the dysfunctional CVAD is critically important to minimize disruption in care and reduce the added risks of additional radiation exposure, anesthesia, and surgery.

Thrombolytic agents have been used during the past three decades as a potential method to restore flow to occluded CVADs in children; however, few prospective studies have been conducted to investigate prespecified techniques and endpoints (2–6). Before 1998, the only thrombolytic agent approved by the U.S. Food and Drug Administration (FDA) for catheter clearance was human-derived urokinase (Abbokinase Open-Cath; Abbott Laboratories, North Chicago, IL). However, the product was withdrawn from the market in November 1998 (7), and no approved product was available until 2001. In September 2001, the FDA approved the use of alteplase (Cathflo Activase; 2-mg/vial, Genentech, South San Francisco, CA) for the indication of restoring function to CVADs as assessed by the ability to withdraw blood (8). The approval was based on the pivotal phase III Cardiovascular Thrombolytic to Open Occluded Lines (COOL) trial (9) and COOL-2 trial (10), but the study population consisted predominantly of adult patients; patients younger than 2 years of age or with a body weight of less than 10 kg were excluded. Because of the scarcity of safety data in children, the FDA requested that an additional postmarketing study be conducted in pediatric patients (11). The Cathflo Activase Pediatric Study (CAPS) was conducted to specifically address the safety and efficacy of alteplase in a pediatric population with dysfunctional catheters.

MATERIALS AND METHODS

Objectives

The primary objective of the study was to evaluate safety, as measured by the incidence of intracranial hemorrhage (ICH) documented by computed tomography (CT) or magnetic resonance (MR) imaging, during the treatment period and within 48 hours after the completion of treatment with alteplase. Two prespecified populations were patients 2–16 years of age and those younger than 2 years of age. The secondary objectives were to estimate the rate of restoration of function to dysfunctional CVADs 30 and 120 minutes after administration of a maximum of two instillations of alteplase and to determine the rate of serious adverse events that occurred within 48 hours of treatment. The serious adverse events studied included major hemorrhage (defined as severe blood loss [>5 mL/kg] or blood loss resulting in hypotension or requiring transfusion), thrombosis, embolic events (defined as any serious embolic event including pulmonary or arterial events [eg, stroke, peripheral, or major organ] or cholesterol plaque), sepsis, catheter-related complications, or any other serious adverse event.

Study Design

The study was a phase IV prospective, open-label, single-arm, multicenter trial conducted at 42 sites in the United States from April 2002 to May 2003 as a postmarketing study that was requested by the FDA and sponsored by Genentech. The request specified that the study consist of at least 250 patients 2–16 years of age and 50 patients younger than 2 years of age (10). The protocol was approved by the institutional review boards at each site, and written informed consent or assent was obtained by a parent, legal guardian, or patient.

Inclusion criteria.—Patients were eligible if they were in clinically stable condition, less than 17 years of age, and had occlusion, defined as withdrawal dysfunction, of a CVAD (includes up to a triple-lumen catheter and ports). For patients who weighed 10 kg or more, withdrawal dysfunction was defined as inability to withdraw 3 mL of blood from the CVAD; for patients who weighed less than 10 kg, withdrawal dysfunction was defined as inability to withdraw 1 mL of blood from the CVAD. If multiple lumens were dysfunctional, the investigator chose one lumen for the study and treated the same lumen with study drug throughout the study. The ability to infuse fluids into the lumen at the volume necessary to instill alteplase was also required.

Exclusion criteria.—Patients were excluded if CVAD function was restored after repositioning, the CVAD was inserted less than 48 hours before enrollment, the CVAD was implanted specifically for hemodialysis, there was evidence of mechanical or nonthrombotic occlusion as determined by the investigator, the patient was previously enrolled in the study, the patient was treated with any thrombolytic agent within 24 hours of enrollment, the patient was at high risk for bleeding events or embolic events (ie, recent pulmonary embolism, deep vein thrombosis, endarterectomy, clinically significant right-to-left shunt) in the opinion of the investigator or had a known condition for which bleeding constituted a significant hazard, or the patient had a known hypersensitivity to alteplase or a component of the formulation.

Treatment protocol.—Alteplase (Cathflo Activase; Genentech) was provided as a sterile vial of lyophilized powder with a concentration after reconstitution with sterile water of 1 mg/mL (7). Each vial contains 2.2 mg alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Patients weighing 30 kg or more were to receive 2-mL instillations (2 mg) of alteplase within the catheter lumen, and patients weighing less than 30 kg were to receive instillations of alteplase equal to 110% of the estimated internal lumen volume of the dysfunctional CVAD (dose rounded to the nearest 0.1 mL, not to exceed 2 mL). Although this was not specified in the protocol, the previous safety study of Cathflo Activase used 10-mL syringes for administration of study medication (10).

Enrolled patients were eligible for serial treatment with a maximum of two instilled doses of alteplase, each with a maximum dwell time of 120 minutes. Assessment of CVAD function occurred 30 minutes after administration of each dose. CVAD function was assessed by first attempting aspiration of blood and, if that was successful, attempting infusion of normal saline solution. Restored function was

defined as the ability to withdraw 3 mL blood and infuse 5 mL normal saline solution in patients weighing 10 kg or more or the ability to withdraw 1 mL blood and infuse 3 mL normal saline solution in patients weighing less than 10 kg. If function was not restored at 30 minutes, another assessment of function was made at 120 minutes. Patients exited the treatment algorithm when restoration of CVAD function was established or after assessment of CVAD function after the 120-minute dwell time for the second instillation, whichever occurred first.

Assessment of safety had two components. All serious adverse events were to be recorded during the treatment period. Additionally, all serious adverse events were to be elicited from all patients or patients' representatives by telephone or in person at 48 hours after completion of the treatment algorithm. The posttreatment contact for the assessment of safety events occurred 48–96 hours after completion of the treatment algorithm. An adverse event was defined as serious if it resulted in death, was life-threatening, required or prolonged inpatient hospitalization, was disabling, resulted in a congenital anomaly or birth defect, may have jeopardized the patient, or may have required medical or surgical intervention to prevent one of these outcomes. Targeted serious adverse events of specific interest included ICH, major hemorrhage, thrombosis, embolic events, sepsis, and catheter-related complications. Screening CT or MR imaging was not performed on patients to exclude an ICH during the treatment period and within 48 hours of treatment. Adverse events that were not serious were not to be recorded.

Statistical Analysis

Safety and efficacy analyses were based on all enrolled patients who received treatment with alteplase (defined as the safety-evaluable population). Treatment was recorded as having occurred in patients who received at least one complete or partial instillation of alteplase.

For the primary safety endpoint of ICH, for each of the secondary safety endpoints (major hemorrhage, thrombosis, embolic events, sepsis, and catheter-related complications), and for the endpoint of any other medically important event, the event rate was calculated and an exact 95% CI was provided. Event rates and corresponding exact 95% CIs were also calculated for the two subgroups of patients less than 2 years of age and 2 years of age or older.

For the primary efficacy endpoint (cumulative restoration rate of CVAD function after a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes) and for each of the secondary and other efficacy endpoints (restoration rate at 30 minutes after the first instillation, cumulative restoration rate at 120 minutes after the first instillation, and cumulative restoration rate at 30 minutes after the second instillation), the restoration rate was calculated and an exact 95% CI was provided. The event rates and corresponding exact 95% CIs were also calculated for the two subgroups: patients younger than 2 years of age and those 2 years of age or older. Patients who did not complete the treatment algorithm were considered to have experienced treatment failure for purposes of the efficacy analyses.

All statistical analyses were performed with SAS software (version 8.2; SAS, Cary, NC). The exact 95% CIs were computed with use of the F distribution method provided by Collett (12).

RESULTS

Demographics

The study population consisted of 310 treated patients (56.1% male and 43.9% female), the majority of whom were white (70.3%), with a mean age of 7.2 years (range, 0.04–18.3 y) (**Table 1**). Fifty-five patients were younger than 2 years of age, and 255 were 2 years of age or older. The overall mean body weight was 30.3 kg (range, 2.2–107.0 kg); 39 patients (12.6%) weighed less than 10 kg.

The most frequent types of CVAD (in descending order) were a port (51.6%), a double-lumen catheter (30.0%), a single-lumen catheter (14.5%), and a triple-lumen catheter (3.9%). By age stratum, the most common type of CVAD in the younger age group was a double-lumen catheter (49.1%) and the most common type in the older age group was a port (59.2%). The primary indications for catheter placement were chemotherapy administration (69.0%), hydration and/or blood transfusion (56.5%), and antibiotic administration (44.5%).

At the time of study treatment, 55% of patients had catheters implanted for less than 90 days and 24.3% had the implanted device for more than 1 year. The majority of patients (81%) received treatment with study drug on the same day that catheter dysfunction was diagnosed.

All enrolled patients were to receive treatment with a maximum of two serially instilled doses of alteplase. Of the 310 enrolled and treated patients, 255 (82.3%) received one dose of alteplase and 55 (17.7%) received two doses. In addition, a total of 282 patients (91.0%) completed the study treatment algorithm and the posttreatment follow-up assessment.

Protocol Deviations

Of the 310 patients, the treatment of 44 (14.2%) involved one or more major protocol deviations. These consisted of CVAD insertion less than 48 hours before enrollment ($n = 2$), high risk for bleeding or embolic events ($n = 2$), age greater than 17 years ($n = 3$), incomplete treatment algorithm ($n = 25$), and incorrect dose ($n = 16$). Incorrect dose was defined as administration of a dose of alteplase that was more than 30% greater than the protocol-specified dose or less than 77% of the protocol-specified dose. Overall, the percentage of patients with major protocol deviations was roughly equivalent in the two age strata (14.5% among patients <2 years of age and 14.1% among patients ≥ 2 years of age). However, for the group of patients younger than 2 years of age, incorrect dosing was the most frequent protocol deviation (7.3%), whereas for the older patient group, incomplete treatment algorithm was the most frequent protocol deviation (9.0%).

Safety Outcomes

The primary safety outcome measure was the incidence of ICH documented by CT/MR imaging during the treatment period and 48–96 hours after completion of the treatment algorithm; however, patients did not un-

Table 1
Demographic Characteristics and Baseline Catheter Information

Characteristic	Age <2 y (n = 55)	Age ≥2 y (n = 255)	Total (N = 310)
Sex			
Male	32 (58.2)	142 (55.7)	174 (56.1)
Female	23 (41.8)	113 (44.3)	136 (43.9)
Race			
White	41 (74.5)	177 (69.4)	218 (70.3)
Black	7 (12.7)	28 (11.0)	35 (11.3)
Asian/Pacific Islander	1 (1.8)	8 (3.1)	9 (2.9)
Hispanic	5 (9.1)	40 (15.7)	45 (14.5)
Other	1 (1.8)	2 (0.8)	3 (1.0)
Mean age (range), y	0.9 (0.04–2.0)	8.6 (2.0–18.3)	7.2 (0.04–18.3)
Mean weight (range), kg	8.0 (2.2–15.2)	35.2 (9.7–107.0)	30.3 (2.2–107.0)
CVAD type			
Single-lumen	15 (27.3)	30 (11.8)	45 (14.5)
Double-lumen	27 (49.1)	66 (25.9)	93 (30.0)
Triple-lumen	4 (7.3)	8 (3.1)	12 (3.9)
Port	9 (16.4)	151 (59.2)	160 (51.6)
CVAD age (d)*			
0–89	46 (83.6)	124 (48.8)	170 (55.0)
90–179	3 (5.5)	21 (8.3)	24 (7.8)
180–364	5 (9.1)	35 (13.8)	40 (12.9)
≥365	1 (1.8)	74 (29.1)	75 (24.3)
Duration of CVAD dysfunction (d)†			
0	40 (72.7)	211 (82.7)	251 (81.0)
1–6	11 (20.0)	34 (13.3)	45 (14.5)
7–13	4 (7.3)	8 (3.1)	12 (3.9)
≥14	–	2 (0.8)	2 (0.6)
Range	0–10	0–84	0–84
Infusion ability‡	43 (78.2)	216 (84.7)	259 (83.5)

* Defined as the number of days from catheter insertion to treatment.
† Defined as the number of days from determination of catheter dysfunction to treatment.
‡ Defined as the ability to infuse 5 mL for subjects weighing ≥10 kg and 3 mL for subjects weighing <10 kg; presented as number and percentage of subjects with infusion ability.
Note.—Values in parentheses are percentages unless specified otherwise.

dergo routine screening CT or MR imaging. No patients experienced an ICH during the study (95% CI, 0%–1.2%).

The secondary safety outcome measures included the incidence of targeted serious adverse events (major hemorrhage, thrombosis, embolic event, sepsis, and catheter-related complications) that occurred any time during the treatment period or within 48–96 hours as determined clinically by the investigator after completion of the treatment algorithm. No cases of major hemorrhage, thrombosis, or embolic events were reported during the study (95% CI for each event, 0%–1.2%). No deaths occurred during the study or the 48- to 96-hour observation period.

Overall, three cases of sepsis were reported (1.0%; 95% CI, 0.2%–2.8%). All three cases were in patients who were at least 2 years of age and who had preexisting infection. The first case was in a 10-year-old patient being treated for Ewing sarcoma who presented with neutropenia, fever/chills, and positive blood culture for Gram-negative bacilli. The patient received alteplase 6 days after admission, and cultures performed on that day were reported to be positive 3 days later. The catheter was then removed, and a culture of the catheter tip revealed an identical organism. This case represented the only case of protocol-defined sepsis. The second case was in a 4-year-old patient with pre–B-cell acute lymphocytic leukemia admitted for fever, neutropenia, fungal sepsis, and renal compromise who had been treated unsuccessfully with alteplase on the day of admission and died of *Candida albicans* septicemia 15 days after study treatment. The third case was in a 13-year-old patient with osteogenic sarcoma in whom progressive bacterial sepsis developed, which was assessed by the investigator to be related to alteplase administration. The patient was admitted with fever and blood cultures positive for *Staphylococcus* species. One day after admission, the patient was treated with two doses of alteplase and experienced hypotension requiring pressor support for 2.5 hours after treatment.

Four patients experienced catheter-related complications (1.3%; 95% CI, 0.4%–3.3%): one patient in the younger age group (1.8%) and three patients in the older age group (1.2%). The first case involved the rupture of the catheter lumen when it was forcibly infused with 0.1 mL of study drug in a patient with a 2-year-old Broviac catheter; this event was assessed by the investigator as related to alteplase administration. For the remaining three cases, no additional details were provided by the reporting investigator.

In total, nine serious adverse events were reported in eight patients (2.6%), two of which were assessed by the investigator as related to alteplase administration (one case of sepsis and one case of a ruptured catheter lumen). These included the four cases mentioned previously and one case of each of the following: fever, tumor lysis syndrome, convulsions/seizures, anxiety attack, and cardiomyopathy.

Efficacy Outcomes

The primary efficacy outcome measure was the overall (ie, cumulative) rate of restoration of CVAD function after serial administration of a maximum of two instillations of alteplase, each followed by a maximum 120-minute dwell time. The overall rates of restoration of catheter function at 30 and 120 minutes were 53.5% and 75.2% and 80.3% and 82.9%, respectively, after the first and second doses. Outcomes were similar among all subgroups (sex, age, CVAD type, body weight) (**Table 2; Figure**).

Table 2
Cumulative Rate of Restoration Catheter Function Overall and by Subgroup

Subgroup	No. of Patients	First Instillation		Second Instillation	
		30 minute Dwell Time	120 minute Dwell Time	30 minute Dwell Time	120 minute Dwell Time
Overall	310	166 (53.5)	233 (75.2)	249 (80.3)	257 (82.9)
Age (y)					
<2	55	24 (43.6)	38 (69.1)	40 (72.7)	44 (80.0)
≥2 to <7	106	58 (54.7)	81 (76.4)	87 (82.1)	89 (84.0)
≥7 to <12	74	38 (51.4)	56 (75.7)	60 (81.1)	61 (82.4)
≥12	75	46 (61.3)	58 (77.3)	62 (82.7)	63 (84.0)
Sex					
Male	174	80 (46.0)	124 (71.3)	136 (78.2)	141 (81.0)
Female	136	86 (63.2)	109 (80.1)	113 (83.1)	116 (85.3)
Body weight (kg)					
<10	39	18 (46.2)	26 (66.7)	28 (71.8)	31 (79.5)
≥10 to <30	160	86 (53.8)	125 (78.1)	132 (82.5)	135 (84.4)
≥30	111	62 (55.9)	82 (73.9)	89 (80.2)	91 (82.0)
Catheter type*					
Single-lumen	45	27 (60.0)	33 (73.3)	37 (82.2)	37 (82.2)
Double-lumen	93	46 (49.5)	70 (75.3)	75 (80.6)	76 (81.7)
Triple-lumen	12	4 (33.3)	9 (75.0)	10 (83.3)	11 (91.7)
Port	160	89 (55.6)	121 (75.6)	127 (79.4)	133 (83.1)

Note.—Values presented are the number (percentage) of subjects in the subgroup with restored function at or before the specified time point.
* If multiple lumens were dysfunctional, the investigator chose one lumen for the study; in this case, restoration of function refers to one lumen only.

DISCUSSION

The management of dysfunctional vascular accesses in sick children can be frustrating and can use significant resources from multiple caregivers, ranging from the primary physician and nursing staff to surgeons, radiologists, anesthesiologists, and phlebotomy/infusion teams. Instillation of a thrombolytic agent has been used in pediatric practice as a noninvasive method to salvage occluded catheters, and numerous retrospective single-center reports have been published, but there are few multicenter, prospective data from larger clinical trials.

Alteplase has been approved by the FDA for the restoration of function to occluded CVADs on the basis of the phase III COOL trials involving 1,135 treated patients (9,10). A total of 126 patients (11%) were 2–16 years of age, and no study drug–related adverse events were reported in this age group. However, there was insufficient enrollment of pediatric patients to enable any firm conclusions to be drawn regarding relative efficacy in the pediatric or low-weight subgroups, relative efficacy related to catheter types used, or relative rates of adverse events (8).

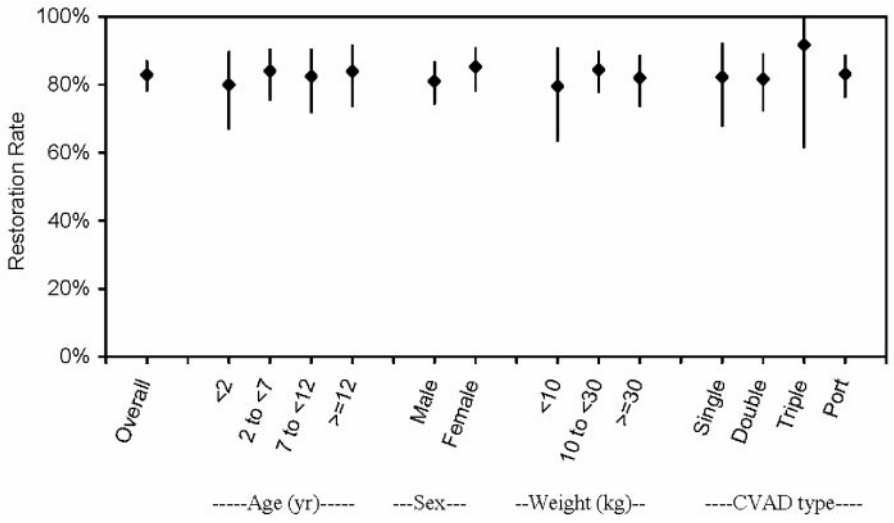

Figure. Cumulative rate of restoration of catheter function after a maximum of two doses of alteplase, overall and by subgroup. Diamond symbol represents observed catheter restoration rate after administration of a maximum of two instillations of alteplase, each with a maximum dwell time of 120 minutes; the vertical bars represent 95% CIs.

Catheter clearance with use of thrombolytic agents typically involves the instillation and filling of the entire dysfunctional catheter lumen with thrombolytic drug. In children, cathe-

ter lengths are variable and are customized by the implanting physician or nurse depending on the anatomy and size of the patient. The lumen volumes are often not precisely known. Instillation of alteplase in the CAPS trial involved slight overfilling of the estimated lumen volume (110%) in children weighing less than 30 kg and a 2-mg dose (2 mL) in all catheters in children weighing 30 kg or more. A small amount of alteplase may have been administered into the systemic circulation. When alteplase is administered according to the study protocol, any circulating plasma levels of alteplase are not expected to reach pharmacologic concentrations (13). The most frequent complication of systemic thrombolysis is bleeding, of which ICH represents the most severe adverse event. The main objective of the current study was to assess the overall safety of a maximum of two instilled doses of alteplase in children.

The results of this study showed that the treatment protocol is safe in children. No pediatric patient experienced ICH, major hemorrhage, thrombosis, or embolic event. In comparison with the COOL trials (9,10), the rates of serious adverse events were similar in pediatric and adult patients.

The most common serious adverse event reported in CAPS was sepsis (1%; $n = 3$). All these patients had evidence of infection before administration of alteplase. Alteplase or any thrombolytic agent should be used with caution in the presence of a known or suspected infection in the catheter. Because evaluation of the catheter involves instillation and flushing, the technique may release a localized infected clot or nonthrombotic debris into the systemic circulation.

The cumulative restoration rates observed in CAPS are similar to those observed in the COOL studies (9,10). The cumulative restoration rates reported in the COOL-2 study (10), which used an identical treatment regimen in 995 patients, were 52% and 75% at 30 and 120 minutes after one dose and 82% and 85% after a second dose, respectively. In this trial, the cumulative restoration rates were 54% and 75% at 30 and 120 minutes after one dose and 80% and 83% after a second dose, respectively. These findings are similar to those of a 2001 report in which alteplase was used to treat 228 children with 320 central venous catheter occlusions (6). In this study, patency was restored in 91% of catheters after one to three treatments. In the current study, the ability for alteplase to restore function was similar among all subgroups, including those based on age, body weight, and catheter type. Therefore, these factors do not appear to play a significant role in the restoration of patency to the occluded catheter.

The CAPS has certain limitations. Treatment of hemodialysis catheters was not evaluated, and therefore the study findings should not be translated to patients with occlusion of these devices. Bamgbola et al (14) have previously noted that low-dose, short-duration alteplase infusions were safe and effective for catheter thrombolysis in children with occluded hemodialysis catheters. In addition, the current study did not examine the use of alteplase for the simultaneous treatment of multiple catheter lumens. Future studies should assess the safety and efficacy of alteplase in patients with multiple-lumen catheter occlusion. In addition, use of shorter or longer alteplase dwell times, including "locking" the catheter with alteplase instead of heparin as a means for prophylactic maintenance of patency in troublesome devices, also was not evaluated (15). Although Weck et al (15) recently reported that 90% of thrombolytic activity was maintained 7 days after alteplase reconstitution with sterile water for injection, further evaluation is warranted before alteplase can be recommended as a locking solution. An incomplete treatment algorithm (caused by missed assessment or missed dose) occurred in 25 patients (8.1%), and incorrect dosing occurred in 16 patients (5.2%). Although these patients were included in the analysis, these results are unlikely to affect the overall efficacy, because an incomplete treatment algorithm would likely decrease the efficacy as underdosing would. Finally, another limitation of this study is that the volume of Cathflo Activase administered frequently exceeded that of the catheter lumen volume (especially in patients weighing <30 kg), which could have resulted in mechanical dislodgement of the catheter occlusion. However, because the efficacy was similar to that observed in the COOL-1 study (9), which was placebo controlled, this is unlikely to have affected the observed efficacy rates.

On the basis of the overall data submitted, the FDA reviewed and amended the prescribing information for Cathflo Activase to include this clinical study (8). In conclusion, the trial results support that the use of alteplase is safe and effective in the restoration of function to occluded CVADs in children and infants.

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