CLINICAL INVESTIGATION

Efficacy and Economic Evaluation of a Volume-Based Cathflo Activase Protocol Versus a Fixed-Dose Alteplase Protocol for Catheter Occlusions in Pediatric Patients

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OBJECTIVES This prospective study evaluated the efficacy and economic benefit of Cathflo Activase and a volume-dependent protocol versus a previously utilized fixed-dose 2 mg/mL alteplase aliquot protocol for central venous catheter clearance in pediatric patients.

METHODS All pediatric patients with a medically diagnosed catheter occlusion were eligible for inclusion into this study. Retrospective data was analyzed from an approved data collection form, which had been implemented during the utilization of the alteplase protocol. Data collection indicators included catheter type, dose, dwell time, outcome of attempt (successful or unsuccessful), additional measures taken, and comments. A new protocol utilizing Cathflo Activase and manufacturer recommended volume-based dosing was prospectively implemented and data was collected and evaluated and compared to data from the alteplase protocol.

RESULTS Alteplase and Cathflo protocol data was evaluated for a total of 96 courses in 48 patients (0.09 – 22.8 years, 2.15 – 105.2 kg). Complete resolution was achieved in 69.6% of patients with the alteplase protocol, partial resolution was attained in 8.7%, and treatment failure occurred in 21.7% of patients. For the Cathflo Activase group, complete resolution was observed in 82% of occlusions, with 8% partial resolution and treatment failure of 10%. The average cost per dose utilized by our patients during this study was $49.68 and $30.56 for the alteplase and Cathflo Activase groups, respectively.

CONCLUSIONS Our data indicate that the Cathflo Activase protocol may be as efficacious as the previous alteplase protocol. Furthermore, there are added time and cost benefits.

KEYWORDS administration, alteplase, catheter occlusions, Cathflo Activase, pediatrics

J Pediatr Pharmacol Ther 2006;11:237–244

INTRODUCTION

Central venous access devices (CVADs) have become increasingly essential in the therapeutic management of chronically ill children. CVADs are used for infusing chemotherapy, blood products, pain medications, long-term antibiotic therapy, and nutritional support.

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ABBREVIATIONS AWP, Average wholesale price; COOL, Cardiovascular Thrombolytic to Open Occluded Lines; CVADs, central venous access devices; IRB, Institutional Review Board; NAVAN, National Association of Vascular Access Networks; SK, streptokinase; t-PA, alteplase; UK, urokinase

Currently, over 5 million CVADs are placed annually.[1] Although essential for quality care,

these devices are associated with a variety of complications, including infection, thrombosis, and dysfunction. Unfortunately, these catheters become occluded as a result of thrombosis at an estimated rate of 25% per year.[2] Catheter occlusions may result in complications and/or removal of the device, resulting in treatment delays, limited treatment options, extended hospitalization, and ultimately increased health care costs.[1]

Urokinase (UK; Abbokinase; Abbott Laboratories) was the first approved thrombolytic agent for restoring function to occluded catheters. Urokinase is a human-derived product which is produced from cells harvested from neonates. In 1999, the Food and Drug Administration (FDA) issued a warning that donor screening was inadequate and may have permitted infectious contamination. As a result, further manufacturing of urokinase was halted and the availability of urokinase was diminished.[3] Streptokinase (SK; Streptase; AstraZeneca) was considered as a possible alternative to urokinase, but its potential for life-threatening anaphylactic reactions deterred it from widespread use.[4] Alteplase (t-PA; Activase; Genentech) is a third thrombolytic agent; it is recombinantly derived and has been shown to be safe and effective in restoring function to CVADs.[5] Alteplase has the advantage of being a biosynthetic material, which is not allergenic and can be administered repeatedly.[6] Alteplase has a high affinity for fibrin-bound plasminogen, which allows it to preferentially activate clot-bound plasminogen, as opposed to plasminogen found freely circulating in the plasma. Therefore, alteplase is highly clot-selective and exhibits increased activity at the site of the clot. In contrast, urokinase and streptokinase are not clot-selective, and induce fibrinolysis by activating all plasminogen found free in the circulation.[1]

There has been minimal to no evidence of intracranial hemorrhage or other systemic hemorrhagic complications such as gastrointestinal bleeding or thrombosis when alteplase is administered to restore patency of occluded catheters.[7,8] Based on studies of efficacy, alteplase has been recommended by the National Association of Vascular Access Networks (NAVAN) as the drug of choice for treating catheter occlusions.[2-12]

At the time of this investigation, alteplase injection was only available as a sterile, lyophilized powder in 50- and 100-mg vials.[13] These larger vials had to be reconstituted using sterile water for injection and divided into smaller aliquots for the treatment of occluded central venous catheters. A majority of institutions utilized 2 mg/2 mL alteplase aliquots which were stored frozen (14 days to 6 months), thawed to room temperature immediately prior to use and then could not be reused.[7,14] There were several limitations to this process, including the utilization of pharmacists' valuable time, occupation of freezer space and potential for large wastage of aliquots.

Within our institution, reconstituted 50-mg vials were divided into individual doses of 2 mg/1 mL alteplase syringes. Each 50-mg vial produced 23 unit dose syringes (accounting for a loss of drug during compounding and transfer procedures), requiring an hour of a pharmacist's time. The individual dose alteplase syringes were stored at a temperature of -20 C° to remain stable for 30 days. The syringes were thawed to room temperature immediately prior to use. Per institutional protocol, each patient with a confirmed catheter occlusion was given a dose of 2 mg/mL. The drug was required to dwell for a period of 2 hours, upon which patency was again tested and determined. If an occlusion was still present, the drug continued to dwell for an additional 2 hours, and a second dose of alteplase was given.

In September 2001, Genentech received FDA approval for alteplase (Cathflo Activase; Genentech) available as single dose 2 mg/2 mL vials to be used specifically for restoring catheter function. Cathflo Activase approval was based on two phase III trials (COOL-1 and COOL-2) performed by the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) investigators in which Cathflo Activase demonstrated a resolution rate of 85%-88% over 30-120 minute dwell times.[2,7] The COOL-1 and COOL-2 trials also demonstrated that an alteplase volume-dependent protocol is safe and effective for catheter clearance in pediatric patients.[2,7] The volume-based protocol in these studies utilized the size or volume capacity of the catheter as basis for the dose of Cathflo to be instilled into CVADs.

Prior to the COOL trials, pediatric experience

with alteplase for catheter occlusions had been limited mostly to empiric dosages from 0.5-2 mg regardless of patient weight, catheter size or age.[12,15] One center reported on its experience with a weight-based dosing strategy that achieved efficacy of 85%.[3] One study conducted in pediatric hematology/oncology patients and cystic fibrosis patients (1.5-27 years) who had either a 9 French implantable port or a double-lumen silastic catheter,[16] reported a 90% success rate with the use of 2 mg alteplase for 4-hr dwell in occluded catheters (n = 6) that had previously failed treatment with urokinase 10,000 units. However, out of the 6 patients who received 2 mg alteplase, only 4 had success with one 2-mg bolus; the other two required 2 and 3 boluses of 2 mg. None of the published pediatric experiences have reported any serious adverse bleeding effects as a result of using alteplase for catheter occlusions.

It was hypothesized that using Cathflo Activase and a volume-based protocol in pediatric patients would reduce initial dwell time, provide equal efficacy in restoring catheter patency, maintain safety and result in decreased cost compared to our institution's standard dose 2 mg/mL alteplase aliquots.

MATERIALS AND METHODS

This was a prospective implementation of a volume-based Cathflo Activase protocol with retrospective non-controlled evaluation of its efficacy versus alteplase aliquot syringes for catheter patency in pediatric patients. Our Institutional Review Board (IRB) reviewed and approved the protocol prior to initiation. Written informed consent was not required by the IRB.

Prior to implementation of the volume-based Cathflo Activase policy, several educational inservices were provided for all nurses. The nursing staff was trained on the reconstitution techniques to be followed when receiving a dose of Cathflo Activase from the pharmacy for the purpose of catheter clearance. The new policy and protocol was reviewed, and all nurses in each of the pediatric units viewed an instructional video on proper administration methods and procedures. All residents and attending physicians received written communication regarding the initiation of the protocol. Data collection forms were also reviewed, and the importance of proper information documentation was emphasized.

All children admitted to our institution who experienced a central catheter occlusion as determined by the attending physician or health care professional were eligible for inclusion in this study. Patients who had a documented history of hypersensitivity to alteplase or its derivatives were excluded from this study. Patients who demonstrated a mechanical obstruction, determined by restoration of catheter patency after mechanical manipulation, were also excluded.

Complete resolution was defined as the ability to aspirate blood and infuse fluids through the venous catheter. Partial resolution was defined as the ability to aspirate blood or flush/infuse fluids with difficulty. Failure was defined as a catheter occlusion that did not resolve after 2 doses of alteplase or Cathflo Activase. Demographic information for each patient including gender, race, weight and age at the time of administration was collected from an electronic database of patient profiles.

After implementation of the new protocol, alteplase or Cathflo Activase was ordered by the physician for catheter occlusions when needed as "per protocol." Orders written for alteplase or t-PA were automatically substituted by the pharmacy for the Cathflo Activase product. The decision to treat the catheter occlusions with a thrombolytic agent remained independent of this study and continued to be physician specific as determined by individual patient needs and clinical status. Mechanical obstruction was ruled out by visual inspection and manipulation of a patient's posture, extremities, or both. The clinical observations indicative of central venous line clotted occlusions included an inability to withdraw blood, an inability or impaired ability to infuse fluid, resistance to flushing, or a sluggish flow.

Un-reconstituted Cathflo Activase was provided by the pharmacy upon receipt of an order for alteplase, t-PA or Cathflo Activase for catheter occlusion via protocol. Cathflo Activase was reconstituted by the nurse per manufacturer recommendations to a final concentration of 1 mg/mL. The appropriate dose of Cathflo Activase to use was specified by our protocol and based on the catheter volume. A

Table 1. Demographics and characteristics of the study population

Characteristic	Alteplase (n = 19)	Cathflo Activase (n = 29)	P-value
Male	16 (84.2%)	14 (48.35)	.027
Weight (kg)*	31.4 ± 26.6	20.8 ± 23.2	.16
Race			
White	9 (47.4%)	11 (37.9%)	.33
Black	9 (47.4%)	18 (62.1%)	
Other	1 (5.2%)	0	
Age (yr)*	6.35 ± 4.37	6.5 ± 6.9	.93

** mean ± SD*

catheter < 3 French was instilled with 0.25 mL, 3-7 French catheters received 0.5 mL, and > 7 French catheters received 1 mL of Cathflo Activase. All implanted ports were instilled with 2 mL. Once Cathflo Activase was instilled in the catheter, the catheter was clamped and was allowed to dwell for 30 minutes. After 30 minutes, the catheter was unclamped and aspiration of blood was attempted. If blood could not be withdrawn or the Cathflo Activase could not be flushed, the catheter was clamped again and allowed to dwell for an additional 30-90 minutes. If the catheter was still not cleared, the first attempt was considered a failure and a second dose of Cathflo Activase from the original vial was repeated using the same procedure.

Data were collected for each patient who received Cathflo Activase during the study period. Data collection indicators recorded by the nurse included CVAD type, dose of alteplase or Cathflo Activase used, dwell time, outcome of attempt (successful or unsuccessful), additional measures taken, and comments. Attempts were defined as the instillation of one dose of alteplase into a catheter or each catheter lumen in multi-lumen devices.

Statistical Analysis

After collection, all data were entered into a database (Microsoft Excel, 2000, Microsoft Corporation) for analysis, and the validity of the data was ensured through review. Descriptive statistics, analyzed with statistical software (Excel Statistical Software Program) were used to asses the demographic information of the patients receiving either alteplase or Cathflo Activase and the doses and dwell times of each attempt in both treatment groups. Two-tailed student t-tests were used to evaluate the interval data available for age, weight, average dose, and average dwell time. A χ^2 analysis was applied to the nominal data gathered for treatment outcomes and ethnicity. The *a priori* level of significance was .05.

RESULTS

Demographics and Efficacy Outcomes

During the eight-month trial period, data was available for a total of 96 courses of treatment administered in 48 patients. We received data collection forms for 24 alteplase patients and 29 Cathflo Activase patients. We were unable to obtain demographic information for five of the alteplase patients, but they were still included in the efficacy analysis. During the Cathflo Activase volume-based protocol period (3 months), 50 doses were dispensed from the pharmacy. Complete data was available for 50 courses of Cathflo Acitvase treatment in 29 patients, and these courses are the basis of this report. Efficacy information was based on the actual number of courses of alteplase and Cathflo Activase administered and not per patient.

Demographic information of treated patients is listed in Table 1. The majority of the subjects in the alteplase group were male (n = 16; 84.2%). The overall mean age in the alteplase group was 6.35 ± 4.37 years (range, 0.4 -13.1 years) with a median age of 5.99 years. The mean body weight was 31.4 ± 26.6 kg (range, 2.15 - 93.4 kg) with a median weight of 20 kg.

Table 2. Efficacy results and outcomes

Characteristics	Alteplase (n = 46)	Cathflo Activase (n = 50)	P-value
Treatment Outcomes			.067
Complete resolution	32 (69.6%)	41 (82%)	
Partial resolution	4 (8.7%)	4 (8%)	
Treatment failure	10 (21.7%)	5 (10%)	
Average dose (mg)*	1.93 ± 0.25	1.03 ± 0.7	<.001
Average dwell time (hrs)*	1.97 ± 0.54	1.41 ± 0.63	<.001

** mean ± SD*

For the Cathflo Activase group, fewer subjects were male (n = 14; 48.3%). The overall mean age was 6.5 ± 6.9 years (range, 0.09-22.77 years) with a median age of 4.27 years. The mean body weight was 20.8 ± 23.2 kg (range, 2.86-105.2 kg) with a median weight of 11.8 kg. There was no significant difference between the groups in age (P = .93) or weight (P = .16).

A cumulative summary of efficacy is presented in Table 2. The proportion of patients in the alteplase group in whom complete resolution was achieved was 69.6%. Partial resolution was attained in 8.7% of the alteplase patients, while treatment failure occurred in 21.7% of patients. The mean dose of alteplase used was 1.93 ± 0.25 mg (range, 1 – 2 mg), with a median of 2 mg. The mean dwell time was 1.97 ± 0.54 hours (range, 0 – 4 hours), with a median dwell time of 2 hours. For the Cathflo Activase treatment group, 82% of patients achieved complete resolution of catheter occlusions. Partial resolution was attained in 8% of the Cathflo Activase patients, and treatment failure occurred in 10% of patients. The mean dose of Cathflo Activase used was 1.03 ± 0.7 mg (range, 0.25-2.2 mg) with a median dose of 0.5 mg. The mean dwell time was 1.41 ± 0.69 hours (range, 0.08-3 hours) with a median dwell time of 1.5 hours. There was a statistically significant difference in the mean dose given (P <. 001) and in mean dwell time (P < .001). Results of a χ^2 analysis of the treatment outcomes indicated no statistical difference in outcome between the alteplase and the Cathflo Activase groups (P = .067).

A sub-analysis was done to compare efficacies based on weight (Table 3). In patients less than 10 kg, complete resolution was achieved in 84.2% of the Cathflo Activase group (n = 19) versus 50% of the alteplase group (n = 4). For patients less than 30 kg (inclusive of the < 10kg group), there was 85% complete resolution in Cathflo Activase group (n = 34) compared to 64.2% in the alteplase group (n = 28). Patients greater than 30 kg achieved complete resolution of 75% and 92.3% for Cathflo Activase and alteplase, respectively.

Cost Analysis

The average wholesale price (AWP) of an Activase 50-mg vial is $1,142.07 (Cardinal Distributors, Inc., 2003). Preparation of 2 mg/mL aliquots yields 23 doses of alteplase from one 50-mg vial, accounting for spills or residuals left in the vial. Using the AWP of the alteplase 50-mg vial, an economic evaluation was performed. The calculated cost for one dose of alteplase is $49.65 per 2 mg/mL syringe. In addition to the AWP price of the alteplase 50-mg vial, this evaluation took into consideration the cost of all supplies used in the manufacturing (syringes and labels) and the cost of 1 hour of pharmacist time to prepare 23 aliquot doses. The total cost of a single alteplase dose is $51.48 per dose, or $25.74 per milligram. The average wholesale price (AWP) of a shipment of Cathflo Activase is $1,186.60 (Cardinal Distributors, Inc.). This purchase provides 20 individual 2 mg/2 mL single use vials. The calculated price for one dose of Cathflo Activase is $59.33 per dose, or $29.67 per milligram. The study results indicated that the mean dose of alteplase given to achieve catheter clearance was 1.93 mg. At the calculated cost of $25.74 per milligram, the total cost of this average dose was $49.68. The study results further indicated the mean dose of Cathflo Activase given

Table 3. Weight-based efficacy sub-analysis

Characteristics	Alteplase	Cathflo
Patients <10 kg	(n = 4)	(n = 19)
Complete resolution	2 (50%)	16 (84.2%)
Partial Resolution	0	2 (15.8%)
Treatment Failure	2 (50%)	0
Patients <30 kg	(n = 28)	(n = 34)
Complete resolution	18 (64.2%)	29 (85%)
Partial resolution	4 (14.2%)	3 (8.8%)
Treatment Failure	6 (21.4%)	2 (5.9%)
Patients >30 kg	(n = 13)	(n = 12)
Complete resolution	12 (92.3%)	9 (75%)
Partial resolution	0	1 (8.3%)
Treatment Failure	1 (7.7%)	2 (16.7%)

was 1.03 mg. At the calculated cost of $29.67 per milligram, the total cost of the mean dose was $30.56 (Table 4).

DISCUSSION

Central venous access devices are commonly placed in children for medication administration, blood sampling, and nutritional support. These devices, although important in therapeutic management of chronically and critically ill children, are associated with a variety of complications, including occlusions. CVAD occlusion may result in a variety of problems, including interruption of the delivery of intravenous therapies, predisposition to catheter-related infection, and extended hospital stay, all of which can increase health care costs.[10] Treatment of CVAD occlusion is less expensive and faster than surgical removal and catheter replacement, with reduced risk of adverse events to the patient. The standard intervention at our institution to restore CVAD patency had been the instillation of an aliquot 2 mg/mL dose of alteplase for 2 hours.

Our study to determine the efficacy of an alternative protocol, implementing Cathflo Activase and a volume-based dosing schedule, showed that Cathflo Activase restored CVAD patency in 88.9% of evaluable courses delivered. Results of a χ^2 analysis demonstrated there was no statistical difference in efficacy outcomes between the alteplase aliquot group and the Cathflo Activase group. The mean dwell time was 1.41 hours, which may indicate that patency can be restored in less time than the previous alteplase protocol recommended. Requiring a mean dose of 1.03 mg in the study displayed that catheter occlusions may successfully be resolved using a smaller dose than the previous alteplase protocol required.

The potential economic impact of selecting Cathflo Activase as a primary agent for catheter clearance was evaluated, and it was determined the average cost per dose of alteplase was $49.68, while the average cost per dose of the Cathflo Activase was $30.56. To interpret this information, however, one must be reminded that while the mean dose of Cathflo Activase was 1.03 mg, the Cathflo Activase vial is always reconstituted to 2 mg/2 mL, leaving 0.97 mL remaining in the vial unused. This remaining amount of active drug has an eight-hour stability after reconstitution and can be used for another catheter clearance attempt, but more often than not, that remaining dose will be wasted. Comparing costs, the AWP of obtaining a dose of Cathflo Activase is $59.33 per vial, while the cost per dose for alteplase, including drug, supplies, and compounding time is $51.48 per dose: a difference of $7.85. What must be considered is the impact on pharmacists' available time while not having to compound and aliquot the alteplase doses. Another consideration is that a vial of Cathflo Activase can be distributed from the pharmacy and again returned if the catheter is determined free of occlusion prior

Table 4. Comparision of cost for Cathflo Activase versus Alteplase

Parameter	Alteplase	Cathflo Activase
Drug Cost*	$1142.07†	$1186.60†
Dose	2 mg/mL	2 mg/2 mL‡
Doses available	23	20
Mean dose	1.93 mg	1.03 mg
Time to prepare	1 hr	NA
Pharmacist salary§	$40.00/hr	NA
Cost of syringe and label	$1.83	NA
Cost per 2 mg dose	$51.48	$59.33
Cost per mg	$25.74	$29.67
Cost per mean dose	$49.68	$30.56

NA (not applicable); USD, United States dollars
** USD*
† Average wholesale price (Alteplase 50 mg/mL and Cathoflo activase 20 x 2 mg/2 mL)
‡ Single use vial
§ average 2003 staff pharmacist's salary at University of South Alabama Women and Children's Hospital

to reconstituting the drug. On the other hand, once a dose of alteplase has been dispensed from the pharmacy, it is thawed within 15 minutes, and if left unused, cannot be returned to the pharmacy and cannot be refrozen. Cathflo Activase vials may eliminate more possibility of waste. Unfortunately, we did not assess whether or not Cathflo Activase vials were utilized for more than one dose or if alteplase syringes were wasted. It is likely that both did occur and would be expected to occur under normal hospital settings. If both did occur, it is even more likely that Cathflo Activase would have greater economic benefit than alteplase syringes. An additional consideration is that the mean doses could differ in other institutions or other studies; the mean doses reported and analyzed were results of this study alone, and may vary.

There are several limitations to this study, impacting the validity of the results. The lack of compliance in completing data collection forms resulted in a very small study population. This study was also limited by its retrospective design and by the fact that the two groups were not concurrent. A retrospective cohort analysis may have been more beneficial in providing data between equally distributed study groups. In addition, a prospective, randomized study would be helpful to confirm these data.

Despite these limitations, the use of our Cathflo Activase volume-based protocol appears to be at least as efficacious as alteplase. Advantages of Cathflo Activase include decreased mean doses, dwell time, cost and pharmacy time. At our institution, the new policy utilizing Cathflo Activase was eventually approved by the Medication Use Committee and implemented.

ACKNOWLEDGMENTS This study has been presented as poster at the American College of Clinical Pharmacy (ACCP) 2003 Annual Meeting, November 4 2003 in Atlanta, Georgia. It has subsequently been published in their Meeting guide and abstracts book.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

REFERENCES

1. Haire WD, Herbst SF. Consensus conference on the use of alteplase (t-PA) for the management of thrombotic catheter dysfunction. JVAD 2000;5:28-36.
2. Ponec D, Irwin D, Haire WD, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: A double-blind placebo-controlled trial-The cardiovascular thrombolytic to open occluded lines (COOL) efficacy trial. J Vasc Interv Radiol 2001;12:951-955.

3. Choi M, Massicotte P, Marzinotto V, et al. The use of alteplase to restore patency of central venous lines in pediatric patients: A cohort study. J Pediatr 2001;139:152-156.
4. Timoney JP, Malkin MG, Leone DM, Groeger JS, Heaney ML, Keefe DL, et al. Safe and cost effective use of alteplase for the clearance of occluded central venous access devices. J Clin Oncol 2002;20;1918-1922.
5. Haire WD, Herbst SF. The use of alteplase (t-PA) for the management of thrombotic catheter dysfunction: Guidelines from a consensus conference of the National Association of Vascular Access Networks (NAVAN). Clinician 2000;18:1-16.
6. Bussieres JF, Therrien R, David M, et al. Efficacy of urokinase and alteplase to reopen occluded central venous catheters in children. J Pharm Technol 2001;17:95-98.
7. Deitcher SR, Fesen MR, Kiproff PM, et al. Safety and efficacy of alteplase for restoring function in occluded central venous catheters: Results of the cardiovascular thrombolytic to open occluded lines trial. J Clin Oncol 2002;20:317-324.
8. Ng R, Li X, Tu T, Semba CP. Alteplase for the treatment of occluded peripherally inserted central catheters: safety and efficacy in 240 patients. J Vasc Interv Radiol 2004;15:45-49.
9. Shen V, Li X, Murdock M, et al. Recombinant tissue plasminogen activator (alteplase) for restoration of function to occluded central venous catheters in pediatric patients. J Pediatr Hematol Oncol 2003;25:38-45.
10. Haire WD, Atkinson JB, Stephens LC, Kotulak GD. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blind, randomized trial. Thrombosis Haemostasis 1994;72:543-547.
11. Semba CP, Deitcher SR, Li X, et al. Treatment of occluded central venous catheters with alteplase: Results in 1,064 patients. J Vasc Interv Radiol 2002;13:1199-1205.
12. Jacobs BR, Haygood M, Hingl J. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. J Pediatr 2001;139:593-596.
13. Genentech, Inc., Activase (alteplase) package insert. South San Francisco, CA; June, 1996.
14. Davis SN, Vermeulen L, Banton J, et al. Activity and dosage of alteplase dilution for clearing of venous-access devices. Am J Health-Syst Pharm 2000;57:1039-1045.
15. Lee EK. Alteplase use for the prevention of central line occlusion in a preterm infant. Ann Pharmacother 2002;36:272-274.
16. Atkinson JB, Bagnall HA, Gomperts E. Investigational use of tissue plasminogen activator (t-PA) for occluded central venous catheters. JPEN J Parenter Enteral Nutr 1990;14:310-311.
17. Genentech, Inc., Cathflo Activase (alteplase) package insert. South San Francisco, CA; September, 2001.