Angioedema Risk Associated With Central Vascular Access Device Declotting

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ABSTRACT

Little is known about the risk of angioedema with low-dose alteplase administration in the treatment of thrombotically occluded central vascular access devices (CVADs). To identify potential cases, the US Food and Drug Administration Adverse Event Reporting System database was searched. Between March 15, 2001, and August 15, 2018, there were 568 low-dose alteplase reports. Of these, 11 appear to be related to complications associated with a device or device occlusion that resulted in an angioedema-like reaction. This suggests that angioedema is a potential complication of alteplase when used for declotting CVADs—a complication that nurses should know how to recognize and treat.

Key words: alteplase, angioedema, Cathflo, central vascular access device, declotting, occlusion, tissue plasminogen activator

Approved by the US Food and Drug Administration (FDA) in 2001, low-dose alteplase, marketed as Cathflo Activase (Genentech, San Francisco, CA), is the standard of care for the restoration of thrombotically occluded central vascular access devices (CVADs), as assessed by the inability to withdraw blood after eliminating other causes of catheter dysfunction.[1,2] Other potential causes of catheter dysfunction include catheter malposition, mechanical failure, constriction by a suture or lipid deposits, and drug precipitates within the catheter lumen.[1]

STUDY OBJECTIVE

Thrombotic occlusions associated with CVAD occlusions are rich in fibrin. Alteplase, a recombinant human tissue plasminogen activator medication, converts plasminogen into the clot-dissolving enzyme plasmin that targets fibrin and causes these thrombotic occlusions to dissolve.[3] Although alteplase is an effective medication for treating thrombotic occlusions, it is known to have serious adverse effects, such as angioedema, when administered in larger and systemic dosages. However, little is known about the risk of angioedema when alteplase is given in a low dose for CVAD occlusions. Therefore, the author sought to evaluate the number of angioedema events associated with the administration of low-dose alteplase (Cathflo) for CVAD occlusions using the publicly available FDA Adverse Event Reporting System (FAERS) database and literature review.[4]

BACKGROUND

Approval of low-dose alteplase for CVAD occlusions by the FDA was based on 2 phase III clinical trials, the *Cardiovascular Thrombolytic to Open Occluded Lines* (COOL) *Efficacy Trial* and the *COOL-2* trial.[5,6] The first trial was a placebo-controlled, double-blind, randomized trial, and the second was a larger open-label trial. In both trials, researchers 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. Both studies enrolled patients whose catheters were not functioning (defined as the inability to withdraw at least 3 mL 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 mL of blood and infusion of 5 mL of 0.9% sodium chloride through the catheter. Patients were

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excluded from the studies if any of the following criteria were met: inability to infuse fluid volume necessary to fill catheter lumen with alteplase, ability to successfully withdraw blood after repositioning patient, devices inserted <48 hours before enrollment, any evidence of mechanical or nonthrombotic occlusion, age <2 years, body weight <10 kg, previous enrollment in study, receipt of any fibrinolytic agent within 24 hours of enrollment, known right-to-left shunt, presence of a patent foramen ovale or other type of atrial/ventricular septal defect, or patients considered by the study investigator to be at high risk for bleeding events or embolic complications or who had a known condition for which bleeding constituted a significant hazard.[5,6]

Current Practice

The current practice for declotting a thrombotically occluded CVAD is based on the 2 COOL studies and is outlined as follows[1,2,5,6]:

1. After ruling out other reasons for catheter occlusion and other contraindications, alteplase is instilled into the catheter at a concentration of 1 mg/mL. For patients weighing ≥30 kg, the recommended dosage is 2 mg/2 mL. For patients weighing ≥10 kg but <30 kg, the dosage is 110% of the internal lumen volume of the catheter, not to exceed 2 mg/2 mL.
2. The drug is instilled into the catheter, where it dwells for <120 minutes and is then withdrawn along with 3 mL of blood.
3. If blood withdrawal is successful, the catheter is then flushed with 5 mL of 0.9% sodium chloride.
4. If catheter function is not restored at 120 minutes after 1 dose of alteplase, a second dose may be instilled following the steps above. Additional readministration of alteplase beyond 4 mg is not recommended, because its efficacy and safety have not been studied.[1]
5. Should serious bleeding in a critical location (eg, intracranial, gastrointestinal, retroperitoneal, or pericardial) occur, treatment with alteplase should be stopped and the drug should be withdrawn from the catheter.

When treatment is administered as recommended, a small amount of alteplase may enter the bloodstream; however, the systemic exposure is low. This remains true even if the entire 2-mg dose is injected into a patient's bloodstream. In addition, given the short half-life of alteplase, endogenous levels of plasmin are reached within 30 minutes of injection in patients weighting ≥30 kg. Reported serious adverse reactions when using low-dose alteplase for treating CVAD occlusions are rare. Although package labeling includes a warning about hypersensitivity, including urticaria, angioedema, and anaphylaxis, the most serious adverse events reported in clinical trials were sepsis (0.4%; presumably from liberating bacteria within lysed thrombi attached to the CVAD), bleeding in the stomach or intestines (0.3% of patients), and blood clots in the veins (0.3% of patients).[1-3,5,7]

Bradykinin-mediated angioedema (eg, laryngeal angioedema) is a rare but potentially life-threatening and hypersensitive complication of alteplase and other medications that can cause the slowdown in bradykinin degradation (eg, angiotensin-converting enzyme inhibitors [ACEIs] that block the renin-angiotensin-aldosterone system).[8] Angioedema is a condition in which the deeper layers of the skin swell because of dilation of blood vessels leading to nonpruritic, nonpitting subcutaneous, and submucosal edema that frequently involves the face and oropharynx (including tongue, palate, and uvula), legs, arms, buttocks, and genitalia but can also involve the bowels. Bradykinin-mediated angioedema can also be caused by an acquired deficiency of the C1-inhibitor, which leads to the uncontrolled production of bradykinin (such as that observed in hereditary angioedema and recurrent angioedema) and may be implicated in at least 1 pathway-associated histamine-mediated angioedema.

Much of the clinical knowledge about alteplase-induced angioedema comes from stroke and cardiac literature. When associated with alteplase, laryngeal angioedema is most commonly associated with larger systemic dosages used in the treatment of acute ischemic stroke, pulmonary emboli, or acute myocardial infarction (maximum dose of 90 mg, 100 mg, and 100 mg, respectively) and when concomitantly used with an ACEI. The incidence of angioedema related to systemic dosing ranges from 0.1% to 5.1%.[9] Reactions usually occur during or within 30 minutes of the end of infusion (which vary based on disease process). Published treatment guidelines for angioedema associated with alteplase are cited from the 2018 American Heart/Stroke Association guidelines for the management of acute ischemic stroke.[10] These guidelines highlight the need to maintain the airway and the potential need for intubation, especially if the edema has a rapid progression (<30 minutes) and involves the larynx, palate, floor of the mouth, or oropharynx. Of course, any infusion of the suspect medications should be immediately discontinued.

Emergency medication recommendations for the treatment of angioedema include the following intravenous medications: methylprednisolone 125 mg, followed by diphenhydramine 50 mg, and followed by ranitidine 50 mg or famotidine 20 mg.[9] If additional treatment is needed, then epinephrine (0.1%) 0.3 mL subcutaneously or 0.5 mL by nebulizer is recommended.[9] Bradykinin-mediated angioedema may be resistant to corticosteroids and antihistamine drugs and may require icatibant, a selective bradykinin B2-receptor antagonist. Icatibant is given as a 3-mL (30 mg) subcutaneous injection into the abdominal area.[9] Additional injections of 30 mg may be administered at intervals of 6 hours, not to exceed a total of 3 injections in 24 hours.[9] Plasma-derived C1 esterase inhibitors may be used if the angioedema is thought to be hereditary or associated with the administration of an ACEI medication.

TABLE 1

Number of Adverse Events Associated With Low-dose Alteplase

	All Reported Adverse Cases (N = 568)		Probable Angioedema Cases Associated With a CVAD (n = 11)		Possible Angioedema Cases (n = 18)	
Year	Event Date (n = 130)	FDA Received Date (n = 568)	Event Date (n = 9)	FDA Received Date (n = 11)	Event Date (n = 11)	FDA Received Date (n = 18)
2018	6	15	2	3	0	1
2017	10	322	0	1	0	2
2016	12	95	0	0	1	3
2015	2	20	0	3	0	3
2014	9	28	1	1	3	3
2013	13	10	0	0	1	0
2012	5	27	0	0	0	0
2011	17	4	0	1	1	0
2010	21	4	3	0	1	3
2009	13	7	0	0	2	0
2008	0	2	0	0	0	1
2007	0	0	0	0	0	0
2006	0	2	0	1	0	0
2005	2	2	1	0	0	0
2004	10	7	0	0	0	0
2003	6	7	0	0	2	2
2002	2	5	2	1	0	0
2001	2	1	0	0	0	0
Missing	438	0	3	0	7	0

Abbreviations: CVAD, central vascular access device; FDA, US Food and Drug Administration.

Table shows the number of adverse events reported to the FDA related to low-dose alteplase administration (Cathflo) for all reasons from 2001 to May 2018 and the latest FDA received date. Data are from the FDA adverse event reporting system.[4]

METHODS

Using a case series study design, the publicly reported FAERS database was searched for adverse event reports, medication error reports, and product quality complaints resulting in adverse events that were submitted to the FDA associated with low-dose alteplase, (referred to as *Cathflo* in the database) between March 15, 2001, and August 15, 2018 (searched on November 28, 2018). These reports were then reviewed for cases associated with a CVAD (eg, device occlusions), and a diagnosis of angioedema or a description of a reaction could reasonably be a result of angioedema (eg, throat swelling with respiratory distress, anaphylaxis, or lip or pharyngeal edema). Isolated cardiac arrest, vascular graft complications without mention of a device, drug errors, problems associated with embolism, and death without mention of other symptoms were not included.

The FAERS database supports the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. Informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonization with coding of adverse events and medication errors using terms from the Medical Dictionary for Regulatory Activities terminology.[11,12] In addition, a review of literature was performed using the following terms: *alteplase* or *Cathflo* AND *angioedema* AND *central* to search PubMed and CINAHL.

RESULTS

A review of the literature produced no specific reports of angioedema associated with low-dose alteplase used for CVAD occlusions. A total of 568 case reports associated with low-dose alteplase reported as Cathflo were entered in FAERS between March 15, 2001, and August 15, 2018 (Table 1). Seventy-seven percent (n = 438) of these cases had missing event dates, and these dates correlate poorly with the initial FDA received date, demonstrating a considerable lag time between occurrence of events and FDA

reporting. The majority of cases have an initial FDA received date between 2014 and 2018 (Table 1), with most events being reported in 2017 (n = 322; 56.7%).[4] Although the increase in 2017 reported adverse events does not correlate with an appreciable increase in possible or probable angioedema cases, there is an increase in probable and possible angioedema cases starting in 2014. These numbers are not adjusted for potential volume changes in alteplase use associated with historical changes in practice and may or may not reflect a change in rates.

Of the reported adverse events associated with alteplase, 11 probable cases were associated with complications related to a device or device occlusion that resulted in angioedema or an anaphylactic reaction (Table 2; data element titled "Reactions" in the database), although only 1 report used the word angioedema.[4] Notes on this case also state that there was a product labeling issue. Outcomes adjudicated as angioedema included the following reactions: angioedema; anaphylaxis; respiratory distress; death with throat irritation; pruritus with dyspnea, skin lesion, peripheral swelling, and chest pain; dyspnea with confusional state, rash, lip swelling, and pharyngeal edema; pruritus with generalized complication associated with device, loss of consciousness, and seizure; and cyanosis, swollen tongue, chest discomfort, lip swelling, and loss of consciousness. An additional probable case associated with CVAD included the word *angioedema*. This patient also received lisinopril, an ACEI, and it is possible (and potentially likely) that the angioedema was triggered by the lisinopril and not the alteplase. Therefore, this case is listed separately as having competing causation. Two additional cases resulting in respiratory failure were listed as possible cases. In addition to alteplase, both cases received midazolam hydrochloride and fentanyl citrate, and it is possible that the sedative agents were the cause of the respiratory failure (as opposed to the alteplase or their use in treating angioedema [eg, an adjunct to intubation]). All but 1 of these 13 cases were considered serious.

An additional 16 cases were adjudicated as possible angioedema cases (Table 2). In these cases, there were competing or other compelling potential causes for angioedema other than declotting of a CVAD, or the reason for alteplase use was unknown. Competing causes included other indications of alteplase, such as in the treatment of an occluded vascular graft or other type of treatment catheter, frostbite, and use during an endovascular procedure. Symptoms in this possible angioedema group ranged from throat irritation to respiratory distress and death. There are 2 cases in this group where the outcome was listed as angioedema and the reasons for alteplase use were unknown. All but 1 of these possible cases were considered serious.

The remaining 538 cases do not appear to be related to angioedema or do not contain enough information to indicate angioedema. Of the 568 reported adverse events associated with low-dose alteplase, there were 61 deaths—32 of which were listed as being catheter related. However, causal mechanisms of death were not reported. Of the 32 catheter-related deaths, 22 were related to a "complication associated with device" or "device occlusion." There were 10 additional deaths where the alteplase was used for an unknown indication.

The majority the 568 reported case reports were submitted by industry after being reported either by a consumer or a health care professional. In written correspondence with a Genentech medical research scientist in 2018, Genentech reported a lack of knowledge of any cases of angioedema associated with low-dose alteplase marketed as Cathflo for catheter occlusions.

DISCUSSION

These results support the assumption that the risk of laryngeal angioedema associated with low-dose alteplase for CVAD occlusions is extremely rare but a potential complication. Although only 11 probable cases were reported in 17 years, further adjudication of these cases and other suspected cases is required to determine causation, as well as the final diagnoses. It is not known if off-label use, such as dosages >4 mg or when used in a manner that results in a higher risk of systemic effects, is associated with a higher risk of angioedema or if the reported events were unrelated to CVAD occlusions, reflecting other clinical indications or other complications of alteplase when used in patients with a CVAD. It is also possible that cases labeled as unknown reason for use that resulted in death or other outcomes are a result of angioedema associated with CVAD declotting. These cases were not captured. Many of the possible cases may or may not be associated with declotting of a CVAD with alteplase and may represent unrelated complications or complications associated with other indications of alteplase use. This is suspected in many of the listed cases.

Although the product insert instructions state that Cathflo Activase is contraindicated in patients with known hypersensitivity to alteplase or any component of the formulation and that angioedema has been reported with use of low-dose alteplase for catheter occlusions, nurses may be unfamiliar with this potentially life-threatening complication. In addition, there is a lack of reported cases in the CVAD peer-reviewed literature, including the 2 COOL studies.

While the angioedema event rate appears to be rare, nurses administering or caring for patients receiving alteplase for catheter occlusions should be knowledgeable about the possibility of such events, the required monitoring to detect events early, and the appropriate emergency treatment. This includes infusion nurses and those nurses working with dialysis or oncology patients with implanted ports, as well as front-line nursing staff who may declot CVADs or manage patients immediately after a declotting procedure.

TABLE 2

Adjudication of Reaction Types Associated With Low-dose Alteplase

Reason for Use	Reactions	No. of Cases
Probable angioedema cases related to declotting of a CVAD (n = 11)		
Complication associated with a device or device occlusion	Severe allergic reactions, such as anaphylaxis, angioedema, or signs suggestive of angioedema plus death with throat irritation	8
Complication associated with a device or device occlusion	Hypersensitivity (1 serious, 1 nonserious)	2
Complication associated with a device	Pruritus, loss of consciousness, and seizure	1
Probable angioedema case with competing causation involving declotting of a CVAD (n = 1)		
Device occlusion, hypertension, product used for unknown indication	Anaphylaxis, angioedema (patient also received lisinopril)	1
Possible angioedema case with competing causation involving declotting of a CVAD (n = 2)		
Complication associated with a device	Respiratory failure with concomitant use of sedatives (midazolam hydrochloride and fentanyl citrate)	2
Possible angioedema cases most likely related to other types of catheter, devices, or procedures other than a CVAD or due to unknown product (n = 16)		
Arteriovenous graft thrombosis, product used for unknown indication	Hypersensitivity and infection	1
Product used for unknown indication	Drug ineffective, hypersensitivity	1
Product used for unknown indication	Dizziness, dyspnea, urticaria and product quality issue (concomitant use of venofer)	1
Complication associated with a device, thrombotic cerebral infarction, vascular graft complication	Acute respiratory distress syndrome	1
Complication associated with a device, frostbite and a graft complication	Fatigue with asthenia, pain, and respiratory disorder resulting in death	1
Complication associated with device, frostbite and graft complication, implant and site reaction, and malignant lung neoplasm	Respiratory disorder along with peripheral neuropathy, pain, edema, asthenia, and fatigue leading to death	1
Device occlusion, hemodialysis complication	Cardiac or respiratory arrest/death	1
Product used for unknown indication	Anaphylactic reaction	3
Product used for unknown indication	Hypersensitivity	1
Product used for unknown indication, multiple sclerosis	Throat irritation	1
Product used for unknown indication	Angioedema and swollen tongue or angioedema	2
Product used for unknown indication, colon cancer, metastases to liver	Pain, dysphagia, peripheral swelling, diarrhea, and thrombosis	1
Catheter management	Blood pressure increased, dyspnea, and chest pain	1

Abbreviation: CVAD, central vascular access device.

Table shows the number of reported angioedema and related events reported to the FDA related to low-dose alteplase administration (Cathflo) associated with devices (assumed to be occluded central vascular access devices) from 2011 to May 2018. Data are from the FDA adverse event reporting system.[4]

For those hospitals that do not have a specific protocol for the treatment of angioedema, the development of an angioedema protocol may be beneficial not only for the nurses working with patients with CVADs but for emergency responders and those working with patients receiving systemic doses of alteplase and other high-risk medications. Staff caring for patients who developed angioedema after receiving low-dose alteplase for CVAD occlusions are encouraged to report their findings in the peer-reviewed literature, as well as to the FAERS database.

LIMITATIONS

Because this study uses secondary data, it has some significant limitations. Reporting adverse events by health care professionals and consumers to FAERS is voluntary and may underrepresent or otherwise misrepresent the number of adverse events associated with low-dose alteplase. Dual reporting can also lead to an overreporting of events. Only manufacturers are required by the FDA to submit reports to FAERS.

Database information has not been verified by the FDA. There may also be variations in product names resulting in further misclassification (eg, reporting problems with systemic doses of alteplase as *Cath Flo*). Information provided is limited. Events reported do not include the total dose used or if the product was used correctly (eg, if the medication was used off-label), and there is no required reporting of concomitant use of other high-risk medication, such as ACEIs.

Importantly, there is no certainty that reported events are causally related to the product; additional information, which is not available from the current data set, is required to make this determination. The type of device associated with each complication is not specifically defined, and the reason for alteplase use is not specifically stated. Alteplase may be used to declot other types of catheters, grafts, and tubes, as well as veins and arteries, and may be given for clinical diagnoses such as myocardial infarction, venous and arterial thrombotic events, and acute ischemic stroke. Errors may be made when contributing a cause by reporters when submitting case reports to FAERS.

In adjudicating cases for this study, the lack of clinical information required subjective judgment in classifying cases. Subsequent reviewers may differ on the categorization of cases.

Information available from publicly reported FAERS is limited. The full reports for each incident were not evaluated because of the prohibitive cost of $270 per record. Because the patient's age was often missing, some of the cases reported could be patients under the age of 18 years. As the number of total catheters treated with low-dose alteplase for CVAD occlusion in the United States per year is not known, it is not possible to calculate incident rates for associated angioedema—therefore, the overall risk is not known. Also, because of the variability of when the cases were reported and entered, and the large number of missing cases, it is not possible to trend data over time.

CONCLUSIONS

The risk of bradykinin-mediated angioedema associated with low-dose alteplase for CVAD occlusions appears rare (with only 11 probable cases reported over the last 17 years) based on voluntary reporting to the FAERS database and a lack of reported events in the peer-reviewed literature. Given the large number of reported nonspecific cases and deaths, along with limitations associated with the FAERS database, a more systematic review of the risk of angioedema with the declotting of CVADs is warranted. Because of the potential seriousness of angioedema, nurses and others caring for patients who receive low-dose alteplase for CVAD occlusions should be aware of the potential complication for these events, their timing, required monitoring, and emergency treatment.

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