Recombinant Tissue Plasminogen Activator for Central Venous Access Device Occlusion

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Maintaining and restoring the function of central venous access devices (CVAD) is an important component of pediatric oncology nursing care. Until 1999, Abbokinase Open Cath (urokinase; Abbott, Abbott Park, IL), a thrombolytic agent was the product primarily used to resolve thrombotic occlusions in intravascular devices. Changes in the manufacturing process mandated by the FDA have resulted in a lack of availability of Abbokinase Open Cath. Recombinant tissue plasminogen activator (TPA) has provided an alternative solution for clearing occluded intravascular devices. This article reviews the literature supporting the use of TPA for CVAD clearance and discusses the process of how to administer the medication. Future implications for research about the use of TPA, and its role in the care of CVADs are discussed.

CENTRAL VENOUS access devices (CVADs) in pediatric oncology patients provide a reliable means of venous access for the administration of medications, blood products, and nutritional support, as well as a source for obtaining blood samples. These devices are at risk for occlusion because of mechanical obstruction, drug precipitation, and/or thrombotic occlusion (Bagnall-Reeb, Ryder, & Anglim, 1994). External mechanical obstructions may include kinked intravenous (IV) tubing, a closed clamp, a clogged injection cap or IV tubing, or constriction of the catheter by the sutures at the exit site. Internal mechanical obstructions may occur if the catheter tip is positioned against the vein, if the catheter tip migrates after placement, or if the catheter becomes pinched against the first rib or clavicle. External obstructions are identified by thorough assessment of the catheter and tubing set-up. Internal obstructions can be identified by chest radiograph to confirm catheter position (Bagnall-Reeb, Ryder, & Anglim, 1994).

Mineral drug precipitates are most commonly caused by medications such as etoposide, calcium, diazapam, phenytoin, and heparin or by lipid solutions found in total parenteral nutrition. Mineral precipitates caused by medications with a low pH should be treated with a 1 mL of 0.1% hydrochloric acid instillation, which is allowed to remain in the catheter for 2 hours. An instillation of sodium bicarbonate (1mEq/mL) should be used to treat medications with a high pH that have precipitated. The institution's pharmacy department is an informational resource on the pH of drug precipitates. Lipid precipitates may be cleared with an ethyl alcohol 70% instillation (Dahl, 1998).

Thrombotic occlusions may occur in as many as 25% of patients with central venous catheters (Bagnall-Reeb, Ryder, & Anglim, 1994). Clotted blood or fibrin within the catheter lumen may develop if the catheter is not flushed adequately or if there is a retrograde blood flow. A fibrin sheath can form and encase the outside surface of the catheter, causing a sac to develop at the distal end of the catheter. A retrograde flow of infusate can then back up the catheter along the length of the sheath (Bagnall-Reeb, Ryder,

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& Anglim, 1994). The fibrin sheath may impede the aspiration of blood from the catheter. Thrombosis formation can also occur at the tip of the catheter, causing catheter obstruction. The thrombosis forms when there is endothelial damage to a blood vessel, which results in a deposit of fibrin (Bagnall-Reeb, Ryder, & Anglim, 1994; Dahl, 1998).

Algorithms for assessment and intervention of intravascular device occlusions have been presented in the literature (Bagnall-Reeb, Ryder, & Anglim, 1994, Dahl, 1998). However, there have been recent changes in pharmacologic products available for clearing thrombotic occlusions. Until 1999, Abbokinase Open Cath (urokinase; Abbott, Abbott Park, IL) was the thrombolytic agent that was primarily used to resolve thrombotic occlusions in CVADs. In January of 1999, the Food and Drug Administration (FDA) identified problems with the manufacturing process of Abbokinase Open Cath (Zoon, 1999). The FDA recommended that Abbokinase Open Cath be restricted to specific patients in which the physician judged Abbokinase to be critical to the clinical situation. In this correspondence, the FDA provided a list of other alternative thrombolytic products that could be considered as alternative treatment options. As a result of the FDA's alert, many institutions have developed new protocols and are relying on new agents for treating CVADs obstructed by thrombotic occlusions. The drug, recombinant tissue plasminogen activator (TPA), has provided an alternative solution for clearing these intravascular devices.

Recombinant Tissue Plasminogen Activator

TPA is a thrombolytic agent used primarily in the treatment of acute myocardial infarction, acute ischemic stroke, and pulmonary embolism. The medication works by binding to the fibrin in a thrombus. It converts the entrapped plasminogen to plasmin resulting in local fibrinolysis (Gardiner-Caldwell Synermed, 1999). In 1987, TPA was approved by the FDA for preventing permanent heart damage immediately after a heart attack. The TPA was found to dissolve clots in 71% of patients who received the drug within 6 hours of the onset of symptoms (Mueller, Rao, & Forman, 1987; FDA, 1987).

A 5-year clinical trial showed that TPA is also an effective treatment for acute ischemic stroke. Patients enrolled in the study had a computed tomography scan to rule out bleeding as the cause of the stroke. Once the ischemic stroke was confirmed, an infusion of TPA was initiated within 3 hours of the initial stroke. The number of patients who received TPA and had favorable outcomes measured at 3 months was statistically significant (The National Institute of Neurological Disorders and Stroke Study Group, 1995; NIH, 1995). The FDA approved the use of TPA to treat stroke in the first 3 hours after onset of symptoms in 1996 (American Heart Association, 1999). The adult dosage of TPA is 100 mg for acute myocardial infarction and pulmonary embolism and 90 mg for acute ischemic stroke. Protocols with infusion rates are specific to the clinical indication.

The most common complication associated with TPA administration in these patients is bleeding. It is difficult to assess the direct relationship between TPA therapy and bleeding risk because the majority of patients are receiving concomitant therapy with heparin and/or other platelet aggregation inhibitors. Bleeding during TPA therapy is most likely to occur at sites of vascular access and is generally not severe enough to require a blood transfusion (McEvoy, 1999). Other potential side effects of TPA administration include hypersensitivity reactions, arrhythmias, nausea and/or vomiting, hypotension, and fever (McEvoy, 1999).

Use of TPA in CVADs

Research studies have shown that TPA is effective in clearing occluded central venous catheters. In a double-blinded randomized trial, Haire, Atkinson, Stephens and Kotulak (1994) compared urokinase versus TPA in thrombosed central venous catheters. They theorized that because TPA has a higher affinity for fibrin than does urokinase, it would be more likely to bind to occlusive thrombi, dissolve the occluding thrombus, and restore

patency. Patients in the study had radiographically proven thrombus obstruction. A dose of 2 mg TPA was calculated to be equivalent to the 5,000-unit dose of urokinase approved by the FDA. In each of the treatment arms, the thrombolytic agent was allowed to remain in the CVAD for 2 hours after it was injected. The dose was repeated if clearance did not come after the first dose. Clearance was confirmed by radiograph contrast injection. The study results showed that TPA restored patency in 25 of 28 catheters (89%) compared with 12 of 22 catheters (55%) with urokinase. The researchers also found that the dose of TPA restored patency more reliably and more rapidly than the standard dose of urokinase. There were no detectable effects on systemic fibrinogen levels measured before and after dosage with either drug, as well as no bleeding complications.

In a Letter to the Editor on the use of TPA for obstructed central venous catheters, Kleta, Schleef, and Jurgens (1998) reported that a single dose of 0.5 mg/0.5 mL of TPA, injected into obstructed CVADs and allowed to remain for 20 to 30 minutes, was generally successful in clearing a thrombotic obstruction. In 5 years, approximately 97% of all obstructed catheters at their institution have been cleared by use of this method (30 to 40 per year). Only four catheters had to be removed due to complete obstruction during the 5-year period. No systemic side effects were observed. The authors stated that TPA seems to be a better and more cost-effective alternative to urokinase.

TPA maintains its sterility and stability for 9 weeks after it is reconstituted under a laminar flow hood, made into 1mg/mL aliquots, and frozen at −30°C (Wiernikowsiki et al., 1999). This process allowed the pharmacy staff to obtain 50 doses from one 50-mg vial, which provided a cost-effective use of an expensive medication. In another study, 25 patients whose ages ranged from 7 weeks to 16 years received 34 doses of TPA for occluded CVADs. The dose ranged from 0.5mg/mL for patients who weighed less than 10 kg to 1 to 2 mg (1mg/mL) for patients who weighed more than 10 kg. The TPA was allowed to remain in the intravascular device for approximately 2 hours. In 28 of the 34 doses (82%), patency was restored in the CVAD. Three of the remaining 6 doses resulted in partial clearance (Choi, Massicotte, Marzinotto, Chan, & Andrew, 1999). Maloney, Hillery, Nelson, and Gill (1999) studied the protein concentration and activity between fresh and frozen 1-mg aliquots of TPA. They found no difference in activity between the fresh and frozen samples. The effectiveness of line clearance was also studied by using two dose levels: 0.25 mg (1 mL) and 0.5 mg (2 mL). Fifty-three patients received TPA for central venous line occlusion, 10 patients received the 0.25-mg dose, and 43 patients received the 0.5-mg dose. The time TPA remained in the line ranged from 0 to 60 minutes. Eighty-nine percent of the lines had patency restored, and 11% of the lines remained occluded. Correlation between dwell time and patency restoration was not reported. Although there was no difference in the effectiveness of the two dose levels, the larger volume was noted to be easier for instillation.

Literature on the use of TPA as a continuous infusion has focused on case reports of infants with catheter-related intracardiac thrombi (Marinez-Tallo, Campo, Delgado, Marfil, & Aguilla, 1997; Giuffre, Compagnoni, Farina, & Mosca, 1998). There are currently no published studies on the use of a TPA infusion for treatment of a fibrin sheath.

At a midwestern institution, a clinical standard for central line clearance using TPA was developed through the coordinated efforts of pharmacy, medicine, and nursing. The pharmacy reconstituted the TPA to a concentration of 1mg/mL, which was then frozen in aliquots. The aliquot doses included 0.5mg/0.5 mL for infant patients (<7.5 kg) and 2mg/2mL for pediatric patients. The cost of a 50-mg vial at the institution was $1,108. Twenty five aliquots were prepared from each 50-mg vial of TPA; therefore, the individual patient did not have to incur the cost of a 50-mg vial when a 2-mg dose was used. When comparing the cost of the new TPA protocol to the old urokinase protocol, the cost for a 2-mg aliquot of TPA was $44.35 compared with a cost of $47.87 when a 5,000-unit vial of urokinase was used.

Application to Practice

Problem solving strategies must be used when there is a CVAD malfunction. These strategies include assessing for mechanical obstruction, repositioning the patient, and asking the patient to cough, deep breathe, and perform the Valsalva maneuver. Re-accessing an implanted CVAD should be considered if needle placement is in question. If the CVAD will flush but blood cannot be aspirated, flushing the line with a 10 mL syringe of normal saline using the "push-pause method" (short, repetitive pushes on the syringe plunger) may be performed. This method of flushing increases turbulence within the catheter lumen keeping residue or clots from adhering to the tubing. If fluid cannot be infused into the CVAD and/or aspirated and clotted blood or fibrin is suspected, TPA can be used in an attempt to clear the line.

TPA is injected using a 10-mL syringe in a sufficient volume to fill the internal volume of the CVAD. An injection cap is attached, and the TPA is allowed to remain in the CVAD for 30 minutes. If the catheter does not clear after 30 minutes, attempts at aspiration may continue every 15 minutes for an hour. If the line still does not clear, an additional 30 to 60 minutes should be allowed to pass before aspiration is attempted again. When aspiration is successful, a 5-mL volume (for pediatric patients) is removed to ensure removal of TPA and residual clot. The line is then flushed with saline using the "push-pause method." If the line does not clear with the first dose, a second dose may be considered. It may be necessary to allow the TPA to remain in the CVAD for 24 hours to lyse the clot.

A venous access device occluded with a blood clot or fibrin may not allow TPA to be injected into it. Excess force may cause dislodgment of the clot or rupture of the catheter. Creating a vacuum to pull the TPA into the line can allow for successful placement. This step is done by attaching a three-way stopcock directly to the hub of the catheter with the "off" valve facing the catheter. An empty 10-mL syringe is placed on the side port of the stopcock, and the TPA dose in a 10-mL syringe is attached to the straight port of the stopcock. With the stopcock open, the empty syringe is aspirated back to the 9-mL mark. The stopcock is then turned open to the TPA syringe. The negative pressure created will pull the TPA into the catheter without force being exerted into the internal lumen of the catheter (Czaplewski, 1998).

Recommendations for Future Research

Currently, Genentech, Inc. (San Francisco, CA) is conducting safety and efficacy studies to acquire data for marketing a single-dose vial of Activase (recombinant tissue plasminogen activator) for catheter clearance (P. Hill, personal communication, January 6, 2000). Research is also needed to evaluate the use of TPA infusions for the treatment of fibrin sheaths because there is currently no published data on dosing, safety, and efficacy.

Conclusion

Recombinant tissue plasminogen activator (TPA) appears to be an effective alternative agent for clearing CVADs occluded with a clot or fibrin. Use of unit dose aliquots makes this a cost-effective solution. Maintaining and restoring the function of CVADs is an important component of pediatric oncology nursing care. Many opportunities exist for continued research about TPA and its therapeutic role in maintaining CVAD patency.

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