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Alteplase (rt-PA) Use in Infants and Children **Marcia L. Buck, Pharm.D., FCCP**

With the recent shortage of urokinase, health care providers have been faced with choosing an alternative therapy for lysis of blood clots. Alteplase, recombinant tissue-plasminogen activator (rt-PA), is currently being used by many practitioners as an alternative thrombolytic. This brief review will focus on the use of alteplase in infants and children.

Mechanism of Action

Tissue plasminogen activator (t-PA) is a naturally occurring protein secreted primarily by vascular endothelial cells.^{1,2} In the body, t-PA catalyzes the conversion of inactive plasminogen to active plasmin. Alteplase is synthetic t-PA produced by recombinant DNA technology. Like endogenous t-PA, alteplase converts plasminogen to plasmin.¹⁻³ Alteplase has a high affinity for fibrin. The alteplase-fibrin complex binds plasminogen at the site of a clot and converts the plasminogen to plasmin, producing local fibrinolysis.³

Indications

Alteplase is currently approved by the Food and Drug Administration for use in the management of acute myocardial infarction, acute ischemic stroke, and pulmonary embolism in adults. It has also been used in patients with unstable angina pectoris, occlusion of small blood vessels by microthrombi, and peripheral arterial thromboembolism. Alteplase has been given to clear thrombi in central venous catheters and to increase perfusion to the extremities of frostbite victims.³

Use in Infants and children

Shortly after the release of alteplase, case reports and small case series began to appear in the literature describing its use in infants and children.^{4,15} In 1990, two case reports were published in *The Journal of Pediatrics*.^{4,5} Kennedy and colleagues described the treatment of a neonate with an aortic thrombus using alteplase.⁴ The patient was the product of a 28 week twin gestation. An umbilical artery catheter was placed on admission to the neonatal intensive care unit. Approximately three days after catheter placement, and one day after an intraventricular hemorrhage (IVH), the infant developed signs of an aortic clot. The authors used an alteplase dose of 0.47 mg/kg/hr for a period of 3 hours, extrapolating from doses recommended for coronary artery reperfusion in adults. Clinical improvement was noted within 20 minutes, and by 90 minutes, pulse strength had returned to baseline. No further extension of the previous IVH was noted.

In that same issue, Pyles and coworkers reported the use of alteplase in a 19 month-old boy with multiple thromboemboli occluding the pulmonary arteries after surgical repair of complex congenital heart disease.⁵ A Swan-Ganz catheter was placed and alteplase was infused at a rate of 0.1 mg/kg/hr for 11 hours. Pulmonary arteriography at 6 and 11 hours showed significant improvement in lung perfusion. No hemorrhagic complications were noted. Despite initial favorable response, the patient expired two months later from severe, acute pulmonary hypertension associated with a large residual thrombus in the left lower lobe pulmonary artery.

Since these two initial reports demonstrating the possible benefit of alteplase in children, other authors have published their experiences. In 1991, Levey and colleagues reported the results of treating a series of 12 children with alteplase after failure of traditional thrombolytics.¹ The patients ranged in age from 1 day to 17 years. Reasons for thrombolysis included clot formation after cardiac catheterization or balloon dilation, central venous catheter occlusion, and Raynaud phenomenon. An additional patient received alteplase intraocularly for clot formation after trabeculectomy. The parenteral doses used ranged from 0.1 to 0.5 mg/kg/hr. In the patient given intraocular alteplase, a dose of 25 micrograms was used. Five patients experienced prolonged bleeding from injection sites. Another patient had a nosebleed during treatment and one 2 month-old child had an upper gastrointestinal tract bleed possibly related to alteplase use.

Other case series have been published which provide similar findings. In 1993, Dillon and colleagues presented four cases of alteplase use in infants.⁶ Their patients included a neonate with congenital nephrotic syndrome who was treated for bilateral renal vein thromboses, a premature infant with a grade I IVH who developed a thrombus in the superior vena cava at the end of a Broviac catheter, and two patients with brachial artery thrombi after catheter placement. The patients were treated with a bolus of 0.1-0.2 mg/kg alteplase followed by an infusion of 0.04 to 0.5 mg/kg/hr. Therapy was continued until clot lysis was detected by ultrasound or angiography. No bleeding complications were noted.

Last year, two additional case series were published in *The Journal of Pediatrics*.^{7,8} Weiner and colleagues from the University of Michigan evaluated seven neonatal cases where alteplase was used for arterial thromboses.⁷ Doses for infusion ranged from 0.1 to 0.5 mg/kg/hr. The average duration of infusion was 25 hours (range 6-39 hours). Complete clot lysis was obtained in four of the patients and partial resolution occurred in two others. Four of the patients experienced bleeding at puncture sites, one patient had a grade II IVH and one had a grade IV IVH and pulmonary hemorrhage potentially related to alteplase therapy. Farnoux and colleagues reported another 16 neonatal cases from University of Paris.⁸ The neonates were treated for thromboses in renal veins, the inferior vena cava, the superior vena

cava, the aorta, the femoral artery, and the innominate vein. All patients were treated with a standard protocol, using an initial bolus of 0.1 mg/kg alteplase given over 10 minutes followed by an infusion of 0.3 mg/kg/hr for three hours. If ultrasound failed to demonstrate clot resolution, the infusion was continued for up to four additional treatment periods. Two patients died without clot lysis. Of the remaining 14, seven had partial responses and seven had complete clot dissolution. Repeat ultrasound up to one week after therapy showed no evidence of clot recurrence.

Among the infants and children treated with alteplase to date, the most common use has been lysis of clots associated with central venous catheters. Localized clot lysis has been considered a distinct advantage of alteplase in these patients, especially premature infants at risk for IVH.⁹⁻¹¹ In 1998, Guiffre and colleagues reported the successful use of alteplase in two premature infants who developed intracardiac thrombi associated with central venous catheters.⁹ One of the patients was born at 27 weeks gestation, weighing only 1 kg; the other was born at 31 weeks gestation. The first patient was treated with a bolus of 1 mg/kg infused over 15 minutes through the catheter, followed by an infusion of 1 mg/kg/hr until resolution was demonstrated on echocardiography at 4 hours. The second patient received 0.5 mg/kg/hr for 6 hours. This regimen was repeated twice over the next two days until clot resolution was proven. Neither patient experienced intracranial bleeding during or after treatment.

In addition to these case series, several more case reports have been published describing alteplase use in the pediatric population. Alteplase has been used successfully in an infant with Kawasaki syndrome who developed a coronary artery thrombus,¹² in a 2 year old child with nephrotic syndrome who developed a pulmonary thromboembolism,¹³ and in a 903 gram premature infant with staphylococcal endocarditis to dissolve a vegetation on the tricuspid valve.¹⁴ Alteplase has also been used in a series of children with widespread microvascular thromboses associated with meningococcal purpura fulminans.¹⁵

Pharmacokinetics

No specific pediatric pharmacokinetic trials with alteplase have been conducted. Data from adult patients suggest extensive distribution, with an initial volume of distribution of 2-5 L. Alteplase is rapidly eliminated by hepatic metabolism, with

a clearance of approximately 3 L/hr and a half-life of 3-10 minutes.^{1,3}

Adverse Effects

Bleeding is the most common adverse effect associated with alteplase use. In adults, the most frequent sites of bleeding reported during clinical trials involved the gastrointestinal tract (5% of patients), the genitourinary tract (4%), and skin (1%). The incidence of retroperitoneal bleeds, epistaxis, and gingival bleeding were all less than 1%.

The risk of intracranial bleeds with alteplase has been correlated with the dose administered. Patients treated with up to 100 mg (or 1 to 1.4 mg/kg in one study) have had a 0.4% incidence of intracranial hemorrhage. The use of the accelerated infusion protocol (infusion over approximately 90 minutes) for patients after acute myocardial infarction increased the risk of intracranial bleeds to 0.7%. Patients treated with high-dose therapy (e.g. 150 mg) had an incidence of 1.4%.³

The incidence of bleeding in pediatric patients has not been established. The case series available at this time suggest a relatively low incidence similar to that seen in adults, however, severe intracranial bleeding has been reported.⁷

Other adverse effects reported with alteplase use in adults include anaphylactoid reactions with laryngeal edema and rash, urticaria, cholesterol embolization, arrhythmias, pulmonary edema, recurrent ischemia and reinfarction, myocardial rupture, pericardial effusion, and cardiac tamponade. These adverse effects appear to be rare and have been most often associated with alteplase use following myocardial infarction. There is also a risk of recurrent thrombosis and embolism after alteplase has been discontinued.³

Dosing Recommendations

Alteplase must be given intravenously. Its large size, 527 amino acids, prevents penetration across tissue membranes. In infants and children, infusions have ranged from 0.01 to 0.5 mg/kg/hr.² While not used in all cases, an initial bolus of 0.1-0.5 may be given over 10 to 20 minutes prior to initiating the infusion.^{6,8,9} During therapy, the dose is titrated according to serum fibrinogen levels, with a usual goal of maintaining levels greater than 100 mg/ml to avoid systemic bleeding. Several authors have recommended obtaining fibrinogen levels every 4 hours until stable, then decreasing the frequency

to once or twice daily.¹⁻³ Prothrombin time (PT) and activated partial thromboplastin time (aPTT) should remain unchanged during alteplase use.

The duration of alteplase infusion is dictated by clinical response. In the case series reviewed, duration of therapy ranged from 1 hour to 14 days. Heparin may be administered after alteplase use to avoid recurrence of thrombus formation, but the efficacy and safety of this regimen has not been thoroughly evaluated in children.^{5,8,13}

Alteplase (Activase®; Genentech) is available in 50 mg (29 million IU) and 100 mg (58 million IU) vials. The lyophilized powder should be reconstituted with sterile water for injection without preservatives to a final concentration of 1 mg/ml. Alteplase may be further diluted with 5% dextrose in water or normal saline prior to administration.³

Summary

With concerns over the safety and availability of urokinase, alteplase has found a greater role in pediatric patients requiring thrombolysis. Alteplase offers the advantages of more localized effects than other thrombolytics and a short duration of effect. While the success of alteplase therapy has been well documented, the risk of bleeding complications is still a great concern. More experience is needed to further define the benefits and risks of alteplase therapy in children.

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Literature Review

Antipyretic pharmacokinetic/dynamic modeling
Pharmacokinetic/pharmacodynamic modeling attempts to predict a patient's response to therapy in order to better determine dose, dosing interval, and resultant serum drug concentrations. The authors of this study compared acetaminophen, ibuprofen, and a placebo in controlling fever curves in 124 children 3 months to 12 years of age. A simple linear relationship between serum antipyretic concentration and temperature was found for some of the patients, but most required the use of a more complex modified sigmoidal model. Variables most highly linked to response were dose administered, patient age, and initial temperature. Children receiving ibuprofen showed a classic dose-dependent response with doses of 5 and 10 mg/kg. As anticipated, the placebo group showed no relationship between dose administered and temperature. While this model does not completely define how antipyretics work in children, it expands our understanding of the complexity of the body's thermoregulatory mechanisms and the effects of our attempts to control them. Brown RD, Kearns GL, Wilson JT. Integrated pharmacokinetic-pharmacodynamic model for acetaminophen, ibuprofen, and placebo antipyresis in children. ***J Pharmacokinet Biopharm* 1998;26:559-79.**

Editors' Note

Welcome to Our New Readers!

The staff of *Pediatric Pharmacotherapy* would like to welcome all new members of the Children's Medical Center staff. This newsletter is provided free of charge to all CMC personnel and referral physicians. If you are interested in submitting material for publication or serving on

the editorial board, please contact Dr. Marcia Buck at the address listed below.

For assistance with questions related to medication use in children currently admitted to the CMC, you may contact the CMC pharmacy at 982-0920. For more in-depth consultations, you may contact Dr. Buck by phone at 982-0921 or by paging 971-6222, or one of the pediatrics pharmacy team members, Clara Jane Snipes, R.Ph. or Doug Paige, R.Ph. by paging PIC 1775.

The University of Virginia Drug Information Center is also available to assist you with medication questions. The Center is run by Drs. Anne Hendrick and Michelle McCarthy. You may contact the Center by phone at 924-8034, Monday through Friday between the hours of 8:00 AM and 4:30 PM. The Drug Information Center can also provide assistance when requesting an addition to the Formulary.

Formulary Update

The Pharmacy and Therapeutics Committee did not meet in July. Meetings will resume in August.

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