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Use of Aminocaproic Acid in Children Undergoing Cardiac Surgery or ECMO

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Antifibrinolytics, such as aprotinin, aminocaproic acid (ACA), and tranexamic acid, are used intraoperatively, postoperatively, and during extracorporeal membrane oxygenation (ECMO) to reduce bleeding and minimize the need for exogenous blood products.[1-3] While aprotinin has been the most extensively studied, its use declined sharply after publication of a multicenter observational study comparing it with ACA, tranexamic acid, and placebo in 4,374 adults which revealed an increased risk of renal failure, cardiac failure, stroke, or encephalopathy in patients receiving aprotinin.[4] Additional study data confirming these adverse effects have recently been made available through Bayer and the Food and Drug Administration.[5] Neither ACA nor tranexamic acid are associated with these risks, making them potentially safer alternatives. This issue of *Pediatric Pharmacotherapy* will review the use of ACA in children and the studies comparing it to other antifibrinolytic agents.

Mechanism of Action

Aminocaproic acid is a synthetic lysine analog that suppresses fibrinolytic activity by fitting into plasminogen's lysine-binding site and preventing the binding of plasminogen to fibrin. In addition, ACA prevents plasmin-mediated degradation of platelet glycoprotein Ib receptors, preserving platelet function.[1-3] It has recently been suggested that ACA also promotes release of endogenous α_2-antiplasmin, which exerts an additional antifibrinolytic effect through neutralization of free plasmin.[6,7]

Efficacy in Reducing Operative Blood Loss

As in studies in adults, ACA use in pediatric patients has been associated with a reduction in operative blood loss, but has not always been found to reduce the need for exogenous blood products. In 1970, Gralnick described the cases of two children with cyanotic heart disease who were given ACA orally prior to surgery and parenterally during surgery.[8] Postoperative blood loss in these children (10 and 20 mL/kg over the first 24 hours) was significantly lower than historical data from 40 untreated children with an average blood loss of 35 mL/kg in the first 12 hours after surgery. In 1974, McLure and Izsak conducted the first pediatric study of ACA, comparing it in 25 children undergoing open heart surgery to 31 controls.[9] Patients randomized to ACA received a loading dose of 75 mg/kg followed by an infusion of 15 mg/kg/hr. Treatment was found to provide the greatest benefit in the 12 children with cyanotic disease, resulting in a 42% reduction in blood loss. Based on their results, the authors recommended that ACA be used in all children with cyanotic heart disease expected to require cardiopulmonary bypass for more than 1 hour.

In 1999, Williams and colleagues from the University of Washington evaluated ACA in 70 high-risk children (all undergoing re-operation or Ross procedures), comparing them to 70 case-controls.[10] The patients in the treatment group received ACA as a 150 mg/kg bolus, followed by a 30 mg/kg/hr infusion. The treated patients had less surgical blood loss (mean 15.6 mL/kg versus 22.2 mL/kg in the controls, $p=0.02$), and fewer required re-exploration for bleeding. Thromboelasticity measurements also showed better preservation of platelet function in the ACA group. There were no differences between the groups, however, in postoperative chest tube drainage, blood products transfused, or blood donor exposures per patient.

In contrast, Rao and colleagues found a significant reduction in postoperative blood loss and transfusion requirements with ACA in their prospective, randomized, placebo-controlled study of 170 children undergoing surgery to repair cardiac defects.[11] The treatment group received three 100 mg/kg ACA boluses: one dose was given IV at induction, the second was given into the pump prime, and a third was given at the time of weaning from bypass. Blood loss at 24 hours was 23.7 ± 5.8 mL/kg in the ACA patients versus 42.6 ± 6.9 mL/kg in controls ($p<0.001$). Total volume of packed red cells given was 10.7 ± 7.8 mL/kg with ACA versus 21.9 ± 7.1

mL/kg in controls ($p<0.001$). There was also a reduction in the amount of platelet concentrate administered (6.2±3.2 mL/kg versus 22.0±6.7 mL/kg, $p<0.001$). The re-exploration rate was also reduced (6% versus 15%, $p<0.001$).

Comparison to Other Antifibrinolytics

Chauhan and colleagues conducted two comparison trials of antifibrinolytics in children undergoing cardiac surgery. In 2000, the authors reported the results of a prospective, randomized, placebo-controlled comparison of aprotinin and ACA.[12] A total of 300 children (2.5 months to 14 years) undergoing cardiac surgery were randomized to receive either low-dose aprotinin (10,000 KIU/kg into the patient and prime, with an infusion of 10,000 KIU/kg/hr), ACA (100 mg/kg into the patient and prime, with an additional dose upon weaning from bypass), the combination of the two agents, or placebo. All three treatment groups produced a significant reduction in postoperative blood loss and transfusion requirements compared to control. Cumulative blood loss at 24 hours was 31±13 mL/kg in the aprotinin group, 32±11 mL/kg in the ACA group, and 29±12 mL/kg in the combination group, compared to 36±19 mL/kg in the controls ($p<0.05$). The authors found no significant differences between aprotinin and ACA, but suggested the combination was slightly more effective than either agent given alone.

It should be noted, however, that ACA does not offer the potential benefit of aprotinin in inhibiting the inflammatory process during bypass.[7] In a study of 72 adults undergoing cardiopulmonary bypass, Greilich and colleagues randomized the patients to receive either ACA, high-dose aprotinin, or placebo in order to study their effects on inflammatory markers.[13] Plasma levels of interleukins were measured prior to surgery, throughout surgery, and during the first 24 hours after surgery. All three groups showed elevations in IL-6 and IL-10 during surgery, but aprotinin significantly blunted the response. Interleukin levels in the ACA patients were no different than placebo. Both aprotinin and ACA reduced blood loss. The authors concluded that both were effective antifibrinolytics, but ACA had no effect on the inflammatory response.

A prospective, randomized study comparing ACA and tranexamic acid use in pediatric patients was published by Chauhan and colleagues in 2004.[14] A total of 150 children (2 months-15 years of age) were enrolled prior to undergoing cardiac surgery. Patients were randomized to receive either ACA (100 mg/kg after anesthetic induction, with another 100 mg/kg while on bypass and a third dose after administration of protamine), tranexamic acid (10 mg/kg at the same three times), or no treatment. The control group had the longest time to sternal closure and the largest overall requirement for blood products. There were no significant differences between the ACA and tranexamic acid groups. Cumulative blood loss at 24 hours was greatest in the control group (36±18 mL/kg), with no difference between the two treatment groups (28±13 mL/kg in the ACA group and 27±14 mL/kg in the tranexamic acid group, $p<0.05$). Re-exploration for increased mediastinal drainage was also highest in the control group (12%), compared to 4% in the ACA group and 2% in the tranexamic acid group. Fibrinogen levels and fibrin degradation product levels were comparable in the two treatment groups. There were no changes in renal function or adverse neurologic events.

Use in ECMO

For more than a decade, ACA has been used to decrease the bleeding complications associated with ECMO.[15-17] In 1993, Wilson and colleagues at Boston Children's Hospital published their early experience with ACA in 42 infants on ECMO, comparing them to a group of 68 controls.[15] The group receiving ACA were given a bolus dose of 100 mg/kg IV at the time of cannulation, followed by an infusion of 30 mg/kg/hr until decannulation. Patients receiving ACA had significantly less bleeding while on ECMO ($p=0.03$) and required fewer exogenous blood products ($p=0.01$). The difference between ACA and control was greatest in the congenital diaphragmatic hernia and cardiac patients, and was not significantly different in the patients with meconium aspiration syndrome. The incidence of intracranial hemorrhage was also significantly different (12% overall in the historical controls, with no cases in the ACA patients, $p=0.007$). There was a trend towards more thrombotic complications in the ACA group, but the difference was not statistically or clinically significant. Based on this report, many institutions implemented ACA protocols for their ECMO patients at high risk for bleeding.

In 1998, Horwitz and colleagues attempted to replicate these results in a prospective study.[16] They conducted a multicenter randomized, placebo-controlled study of ACA in 29 infants on ECMO. Thirteen neonates were randomized to receive ACA as a 100 mg/kg IV bolus followed by a 25 mg/kg/hr infusion for 72 hours, and 16 received placebo. Although the results were not statistically different, there was a higher incidence of intracranial hemorrhage in the patients receiving ACA (23% versus 12.5% in controls). Thrombotic complications developed

in two patients, both in the placebo group. The authors concluded that ACA did not appear to decrease the risk of intracranial hemorrhage.

In 2003, Wilson's group published a ten-year retrospective review of their cumulative experience with ACA in high risk neonates on ECMO.[17] During the period from 1991 to 2001, 431 neonates were placed on ECMO. Of those, 298 patients (69%) were given ACA. The most frequent reason for use was the need to perform surgical procedures during ECMO. Comparing the results of their ACA patients to cumulative patient data from the Extracorporeal Life Support Organization (ELSO) registry, the authors found no significant difference in the rate of intracranial hemorrhage, but there was a significant reduction in blood loss associated with surgical procedures (10% in the ACA patients versus an average of 30% in the ELSO registry data). The rate of thrombotic complications was no different between the ACA patients and controls from their institution (cerebral infarction 4% versus 5% and vessel thrombosis 3% versus 1%). The ACA patients required more frequent circuit changes and were on ECMO for a significantly longer period of time. The authors concluded that although ACA did not reduce intracranial hemorrhage, it was effective in reducing surgical blood loss. They suggested that ACA may be most beneficial in postcardiotomy patients, who appear to be at greatest risk for surgical site bleeding.

Adverse Effects

The most serious complication of ACA use in surgical patients is thrombosis, with resultant loss of grafts, myocardial infarction, stroke, or pulmonary embolism.[7] Although limited data are available on thrombosis after ACA use in cardiac patients, pooled analysis of four clinical trials in adults revealed a statistically significant increase in perioperative myocardial infarction (OR 2.5, 95% CI 1.06-5.86, $p = 0.035$).[1] In an analysis of 6,296 patients undergoing CABG, the incidence of stroke was no higher in the 3,135 patients receiving ACA than in those who did not (1.3% versus 1.7%).[18] In the clinical trials conducted in pediatric patients to date, no significant adverse effects have been reported.

Fatal thrombosis has been reported with ACA use in both children and adults.[19,20] Hocker and Saving reported fatal aortic thrombosis in a neonate receiving ACA during ECMO.[19] In 2001, Fanashawe, Shore-Lesserson, and Reich reported two fatal cases of thrombosis in patients given ACA during deep hypothermic circulatory arrest.[20] Both patients were adults undergoing aortic replacement surgery and had received ACA as a 150 mg/kg bolus followed by a 15 mg/kg/hr infusion. Both died of aortic thrombosis, within hours of surgery.

Administration of ACA may produce intrarenal obstruction as a result of glomerular capillary thrombosis. Aminocaproic acid should not be used in patients with hematuria or known renal disease, unless the benefits clearly outweigh the risks. Other adverse effects reported with ACA use in the perioperative setting include: bradycardia, hypertension, hypotension, peripheral ischemia, intracranial hypertension, headache, rhabdomyolysis, thrombophlebitis, myositis, and hypersensitivity reactions.[1,3]

Dosing Recommendations

In children undergoing cardiac surgery, ACA has been administered either by continuous infusion or intermittently. Several early studies used a regimen consisting of a bolus of 75 to 150 mg/kg ACA, followed by an infusion of 15 to 30 mg/kg/hr.[9,10] This regimen has also been used for administration during ECMO.[15-17] More recent studies conducted during cardiac surgery have used intermittent dosing, with a dose of 100 mg/kg ACA given after induction, a second dose given while on bypass, and a third dose given over 1 to 3 hours after the completion of the case or the administration of protamine.[11,12,14]

While the optimal dosing regimen remains to be determined, some authors have suggested incorporating components of both the intermittent and infusion methods into one regimen. Ririe and colleagues at Wake Forest recently conducted a pharmacokinetic modeling study in eight children (9 months-4 years of age).[21] Based on their analysis, the authors propose an ACA regimen consisting of a dose of 75 mg/kg given IV over 10 minutes at induction, along with a 75 mg/kg dose into the bypass circuit prime, followed by an infusion of 75 mg/kg/hr. Clinical studies have not yet been conducted to validate this regimen.

Aminocaproic acid should be diluted prior to administration. Sterile water for injection, normal saline, 5% dextrose, or Ringer's injection may be used to dilute ACA to a final concentration of 20 mg/mL.[3]

Availability and Cost

Aminocaproic acid is available as both brand (Amicar®; Immunex) and generic products. The average wholesale price (AWP) for a generic brand is $1.31 for a 20 mL (250 mg/mL) vial. For comparison, the AWP for aprotinin is $594.31 for a 200 mL (10,000 KIU/mL) vial.[22]

Conclusions

The use of ACA has been associated with a reduction in intraoperative and postoperative blood loss in several studies of children and adults. It has also been found to be beneficial in neonates requiring surgery while on ECMO. Although not as effective as aprotinin in some studies, in other analyses ACA has been found to provide comparable benefit. Unlike aprotinin, ACA does not provide an inhibitory effect on the inflammatory response, but it offers the advantage of being considerably less expensive and does not carry the risk of sensitization to foreign proteins. In routine pediatric cases where the anti-inflammatory properties of aprotinin are not likely to produce additional benefit, or in patients at risk for hypersensitivity reactions to aprotinin, ACA may be the antifibrinolytic of choice.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 9/29/06:

1. Varenicline (Chantix™) was added to the Formulary as an aid for smoking cessation.
2. Darunavir (Prezista™) was added for the treatment of HIV infection in antiretroviral-experienced patients such as those with HIV-1 strains resistant other protease inhibitors.
3. Lanthanum carbonate (Fosrenol®), a rare earth element that binds dietary phosphate, was added to the Formulary for patients with end-stage renal disease. It is restricted to use by Nephrology.
4. Natalizumab (Tysabri®) was added for the treatment of patients with progressing relapsing remitting multiple sclerosis who have failed or are intolerant of conventional therapies.
5. Rifaximin (Xifaxin™) was added with restriction to Gastroenterology for treatment of hepatic encephalopathy.
6. Mexiletine and perphenazine were returned to the Formulary due to frequent requests.
7. The restriction on dexmedetomidine was amended to include all ICU attending physicians.

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