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Antithrombin Administration during Pediatric Extracorporeal Membrane Oxygenation

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Optimal management of anticoagulation during extracorporeal membrane oxygenation (ECMO) in infants and children remains controversial.[1,2] A survey of 121 ECMO centers published last month in *Pediatric Critical Care Medicine* found considerable variation among programs in both therapies and monitoring.[3] This variation is based not only on differences in clinical experience but also on the continued integration of technologic improvements in circuit components as well as adoption of new techniques for monitoring coagulation status.

Antithrombin has long been used to optimize heparin therapy and provide a more consistent state of anticoagulation during ECMO, with a goal of reducing clot formation in the circuit, improving its durability and decreasing the need for circuit manipulation, while minimizing the risk for hemorrhage.[1] In the recent survey, 82% of centers monitor antithrombin activity in their ECMO patients. In patients with levels below the desired range, over two-thirds use exogenous antithrombin in addition to fresh frozen plasma to supplement.[3] Despite our clinical experience, there has been relatively little research published in this area until recently. New papers suggest an improvement in patient outcomes using a more intensive management strategy which includes frequent antithrombin supplementation.

Mechanism of Action

Four forms of antithrombin were described by Seegers and colleagues in the 1950s.[3] Antithrombin III, the active form of antithrombin, is an $alpha_2$-glycoprotein found in human plasma at a concentration of approximately 12.5 mg/dL. In clinical practice, the terms antithrombin and antithrombin III are used interchangeably. Antithrombin is a serine protease inhibitor. It forms an irreversible covalent bond with coagulation enzymes, primarily thrombin and factor Xa, creating a complex that renders them inactive. Antithrombin can also inactivate plasmin, as well as factors IXa, XIa, and XIIa, but to a lesser degree. Antithrombin activity is measured as a percentage of normal (100%).[1,4,5]

Neonates are known to have low levels of antithrombin activity. Adult values typically are not reached until at least 3 to 6 months of age.[6] In 2009, Newell and colleagues evaluated antithrombin levels in a small sample of children enrolled in an observational study of heparin monitoring.[7] They reported a mean antithrombin level of only 45±15% in the 14 infants, with an average of 71±17% in the four children over 1 years of age. Similar results were reported by Bembea and colleagues in the January 2013 issue of the *ASAIO Journal*.[8] In a study of 34 infants and children receiving ECMO, patients less than 30 days of age had a median antithrombin level of 57%, significantly lower than the median value of 64% in the patients 5 months to 15 years of age ($p = 0.007$).

Heparin potentiates the effect of antithrombin, increasing its ability to inhibit thrombin and factor Xa by up to 10,000-fold. Heparin binds to antithrombin, making a conformational change that increases the rate at which it inhibits serine proteases. Inadequate antithrombin levels reduce the effectiveness of heparin and result in higher heparin dosage requirements in order to produce systemic anticoagulation.[1,3,4,5]

Pharmacokinetics

Antithrombin is available in both human and recombinant forms. The pharmacokinetic profiles of both products have been evaluated in adults with hereditary antithrombin deficiency. The half-life of human antithrombin is approximately 2.5-3.8 days. Recombinant antithrombin has a clearance of approximately 7-10 mL/kg/hr and a half-life of 11.6-17.7 hrs.[4,5]

Clinical Studies

The role for antithrombin in the anticoagulation of ECMO patients is not clearly established. The frequency of supplementation as well as the dose vary among programs, ranging from intermittent monitoring and supplementation to the use of a continuous antithrombin infusion. Agati and colleagues were among the first clinicians to describe an intensive anticoagulation strategy that incorporated greater antithrombin use. They evaluated 11 children receiving ECMO after

undergoing surgery with cardiopulmonary bypass.[9] Seven patients were treated prior to modification of their anticoagulation program and six treated after the change. The first group was managed with traditional heparin therapy (10-20 units/kg/hr) and given bolus doses of antithrombin to maintain levels greater than 60%. The last six patients received antithrombin as a continuous infusion starting immediately after surgery. Antithrombin levels were checked every 4 hrs and the infusion was adjusted to maintain a level of 100% or greater. Low-dose heparin (2 units/kg/hr) was started when the antithrombin level had been stable for at least 12 hrs. All patients were monitored with ACT, aPTT, and fibrinogen levels, as well as thromboelastography.

The authors reported better control of coagulation in the second group. Three patients in the first group died, with two having severe hemorrhagic neurologic events. The remaining eight patients survived to discharge, with three requiring surgical revision to correct bleeding while on ECMO. There were no cases requiring surgical revision or thromboembolic events in the second group. The authors suggested that their new strategy may reduce excessive bleeding and minimize the need to return to surgery.

An intensive anticoagulation monitoring regimen was also used by Sievert and colleagues in a case report of a 20-month-old female placed on ECMO for respiratory failure associated with influenza.[10] Coagulation status was monitored with aPTT and ACT. After developing pleural effusions and a thrombus in her inferior vena cava, she was found to have a low aPTT and subtherapeutic anti-Xa levels in spite of an increase in the heparin infusion. An antithrombin level was 40%. Administration of recombinant antithrombin produced improvement in her antithrombin level, aPTT and anti-Xa values. At that point, the decision was made to monitor both antithrombin and anti-Xa levels more closely. Subsequent doses of antithrombin were administered to maintain a level greater than 60%. The patient had no further signs of either thrombosis or excessive bleeding. She was weaned off ECMO on hospital day 33 and later discharged to home. The authors suggested that more extensive monitoring of coagulation, in addition to antithrombin supplementation, may improve outcomes in longer ECMO cases.

The safety of antithrombin administration during pediatric ECMO was evaluated by Niebler and colleagues in a retrospective review of 28 infants and children (1 day to 19 years of age).[11] The authors reviewed data from a 3-year period to evaluate the effect of supplementation on heparin dosing and the potential for increased hemorrhagic complications. Antithrombin was administered for levels less than 80%, with the timing and dose determined by the treating physician. Although some patients received multiple doses, the authors evaluated only the results of the initial dose. As expected, the mean antithrombin levels at 8 and 24 hrs post-dose were significantly higher than baseline (96.8$\pm$25.6% and 92.0$\pm$18.2%, respectively, compared to 61.5$\pm$13.0%, $p < 0.001$). Heparin infusion rates before and after therapy, however, were not significantly different. In spite of the potential for greater anticoagulation with the addition of antithrombin, there was no indication of an increase in bleeding. There was no significant difference between pre- and post-dose values for either chest tube output or packed red blood cell (pRBC) requirement. The incidence of intracranial hemorrhage and survival to discharge were no different in these patients compared to ECMO patients treated before the introduction of antithrombin. The authors concluded that antithrombin did not increase the frequency of bleeding and that supplementation warranted further investigation.

In their 2013 observational study of anticoagulation monitoring in 35 courses of ECMO, Bembea and colleagues noted that antithrombin supplementation was used in nine (26%) of the cases.[8] The patients received between one and six doses, with a median dose of 40 International Units/kg. The median baseline antithrombin level for all patients was 43%, with a range of 38-64%. In the patients receiving antithrombin, the median level after treatment was 65%, significantly higher than that of the patients who did not receive treatment (56%, $p < 0.001$). The authors found an inverse correlation between antithrombin levels and activated clotting time (ACT); for each 1% increase in antithrombin, the ACT was shorter by 0.6 sec (95% CI 0.4-0.4%, $P < 0.01$, $r = -0.33$). Antithrombin levels had a weak correlation to heparin infusion rates ($r = 0.15$), but a strong correlation with anti-Xa levels ($r = 0.57$). For every 10% increase in antithrombin, anti-Xa increased by 0.08 International Units/mL (95% CI 0.07-0.1 International Units/mL, $p < 0.001$).

Several recent abstracts have added to our understanding of the benefits and limitations of antithrombin use. Chernoguz and colleagues at Cincinnati Children's Hospital presented the results of a retrospective study of 11 infants with congenital diaphragmatic hernia (CDH) on ECMO at the 2011 American Academy of Pediatrics meeting.[12] Patients were divided into two groups: five who received a continuous infusion of antithrombin (mean level 86.4$\pm$2.84%) and six who did not. Information on dosing was not provided. Patients receiving continuous antithrombin had a significantly

greater period of time with therapeutic anti-Xa levels (64.9±4.2% versus 29.1±8.6%, p = 0.008), as well as fewer changes in heparin dose (2.38±0.36 versus 6.48±0.88 changes/day, p = 0.005). There was no difference in the incidence of bleeding. The authors concluded that continuous antithrombin administration provided more consistent anticoagulation without increasing the risk for hemorrhage.

Similar results were reported by Perry and colleagues at the 28th Annual Children's National Medical Center ECMO Symposium in 2012.[13] They compared 11 children with CDH on ECMO prior to routine use of antithrombin and 12 children after initiation of antithrombin replacement at Children's Hospital Los Angeles. In the first 3 days of ECMO, the patients given antithrombin received 26% less fresh frozen plasma, 30% less platelets, and 68% less pRBC. The authors concluded that supplementation of antithrombin when levels are less than 60% can result in clinically significant reductions in blood product exposure.

In contrast, Brynes and colleagues at the University of Arkansas found no significant change in heparin infusion rates with administration of antithrombin during pediatric ECMO.[13] They evaluated 47 ECMO courses in 46 children. Antithrombin levels were assessed daily and supplementation was given for levels less than 70%. The authors' primary outcome measurement, the percentage of patients with at least a 10% reduction in heparin rate, was not significantly different in those who received antithrombin and those who did not (38.4% versus 32.9%, p = 0.52). The authors also reported that supplemental antithrombin did not improve circuit durability.

Warnings and Precautions

Although highly purified during the manufacturing process, human antithrombin carries the risk for transmission of infectious agents. No cases of viral disease or Creutzfeldt-Jakob disease have been reported with human antithrombin use. Recombinant antithrombin does not pose this risk, but it is contraindicated in patients with a history of hypersensitivity to goat or goat milk proteins, which are used in its production.

Adverse Effects

The most significant adverse effect of antithrombin use during ECMO has been excessive bleeding. In patients with hereditary antithrombin deficiency, the most commonly reported adverse effects after antithrombin administration include dizziness, nausea, chills, abdominal pain, difficulty breathing, chest pain, blurred vision, hematomas, fever, urticaria, and infusion site reactions (all occurring in ≥ 5% of patients). Serious reactions in this patient population have been rare, but include intra-abdominal hemorrhage and hemarthrosis.[4,5]

Drug Interactions

The administration of antithrombin to patients receiving a heparin product is expected to increase the activity of the heparin. Heparin dose reduction, guided by ACT, aPTT, or anti-Xa levels, is needed to maintain optimal anticoagulation while minimizing the risk for excessive bleeding. All heparins, including unfractionated heparin or low-molecular-weight heparins, may alter the half-life of antithrombin.[4,5]

Availability and Cost

Antithrombin is available as human antithrombin III (Thrombate III®, Grifols Therapeutics Inc.) and recombinant antithrombin (ATryn®, GTC Biopharmaceutics). Thrombate III® is available as a lyophilized powder. When reconstituted with sterile water, each single-use vial contains approximately 500 International Units of antithrombin per 10 mL. It is prepared from pooled donor plasma, with a multistep process for isolation and purification. The use of human plasma results in small variations in the amount of antithrombin activity per vial, so each vial is labeled with its exact content.

Recombinant antithrombin (ATryn®) is prepared from the milk of genetically engineered goats. The DNA coding sequence for human antithrombin is introduced into a mammary gland specific DNA sequence which directs the expression of antithrombin in the goat's milk. Recombinant antithrombin is available as a lyophilized powder in single use vials containing 1,750 International Units of antithrombin activity per 10 mL. Both human and recombinant antithrombin are priced by International Unit because of the variation per vial. The average wholesale price is $4.30 per International Unit for Thrombate III® and $2.34 for ATryn®.

Dosing Recommendations

Traditionally, antithrombin III dosing has been based on the following equation, using the patient's weight in kg and a desired antithrombin level (%AT) between 80% and 120%:

$$\text{Units Needed} = \frac{[\text{desired \%AT} - \text{baseline \%AT}] \times \text{weight}}{1.4}$$

This equation was derived for antithrombin replacement in patents with hereditary antithrombin deficiency and may not be optimal for supplementation during ECMO. As recent papers suggest, higher doses may be necessary to see significant benefit. Antithrombin may be given as an intermittent IV dose, infused over 10-20 min, or as a continuous infusion. Both human

and recombinant antithrombin can be administered through peripheral or central IV access. There is no information available on their compatibility with other medications. Additional doses should be guided by serum antithrombin levels as well as other indices of coagulation status. The timing of antithrombin levels in infants and children on ECMO has not been well established. Monitoring is often done on a regular 12 or 24-hour basis to identify the need for redosing. The minimum acceptable level varies among centers, with most using a value between 60 and 100%.[3-5]

Summary

Antithrombin is essential for optimizing the effectiveness of heparin. Administration of antithrombin during ECMO has been shown to reduce the dose of heparin required and produce more consistent anticoagulation in some studies, without increasing the risk for excessive bleeding. A variety of administration techniques have been reported, ranging from traditional intermittent administration to use of continuous infusions. The latter method has recently been proposed as a more effective delivery mechanism and may reduce drug waste. More studies are needed to establish the best method for using antithrombin in pediatric ECMO.

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Formulary Update

The following actions were taken at the December and January meetings of the Pharmacy and Therapeutics Committee:

1. Gadobutrol (Gadavist™) was added to the formulary for diagnostic MRI in children and adults being evaluated for a disrupted blood brain barrier and/or abnormal vascularity in the central nervous system.
2. Ziv-aflibercept (Zaltrap®) was added for relapsed metastatic colorectal cancer.
3. Disopyramide phosphate immediate release was added to the formulary for treatment of hypertrophic obstructive cardiomyopathy.
4. Choline magnesium trisalicylate was added to the formulary.
5. Polyethylene glycol-based bisacodyl suppositories were added for the treatment of constipation in patients with spinal cord injury. Use of this product has been shown to reduce time to bowel evacuation by 50% compared to standard bisacodyl preparations.
6. Pediarix® was approved as an alternative to Pentacel®.
7. The restriction on budesonide capsules was amended to include treatment of graft-versus-host disease.
8. The restriction on mercaptopurine limiting use to established acute lymphatic leukemia was removed.
9. Diclofenac was removed from the formulary.

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