

# Cardiopulmonary Bypass Using Argatroban as an Anticoagulant for a 6.0-kg Pediatric Patient

Brian Mejak, BS, CCP; Carmen Giacomuzzi, BSN, CCP; Irving Shen, MD; Lynn Boshkov, MD; Ross Ungerleider, MD

*Pediatric Cardiac Surgery, Doernbecher Children's Hospital, Oregon Health and Science University, Portland, Oregon*

**Abstract:** A patient was born with transposition of the great arteries, double-outlet right ventricle, interrupted aortic arch, and a ventricular septal defect and underwent a Damus-Kaye-Stansel procedure with a modified Blalock-Taussig shunt at 14 days old. Three months later, this patient presented with hypoxia and bradycardia was found to have a thrombus present in the main pulmonary artery extending to right pulmonary artery. After initiation of thrombolytic therapy, the patient became severely hypoxic and required the institution of extracorporeal membrane oxygenation. As the result of unknown heparin re-

sistance independent of adequate antithrombin III levels, argatroban therapy was used to achieve desired anticoagulation. The patient was taken to the operating room and converted to conventional cardiopulmonary bypass once adequate activated clotting times were achieved using argatroban. This case report summarizes the use of argatroban as an anticoagulant for a 6.0-kg pediatric patient undergoing cardiopulmonary bypass. **Key-words:** cardiopulmonary bypass, pediatric, argatroban, thrombolysis, anticoagulants. *JECT. 2005;37:303-305*

Heparin can elicit a wide range of immunologic responses when used for cardiopulmonary bypass (CPB). Heparin-induced thrombocytopenia (HIT) is one reaction in which antibodies develop to the heparin/platelet factor 4 complex after being exposed to heparin. Prevalence of heparin-dependent antibodies has been reported in 25-50% of postcardiac adult population, and current literature suggests HIT is underreported in pediatric/neonatal patients with congenital heart disease (1). Platelet clumping and arterial and venous thrombi may occur in these patients. These clinical symptoms mainly reveal themselves 1-4 days after heparin use and can be associated with high morbidity and mortality if not treated (1). If HIT is detected early enough, these clinical symptoms generally can be avoided or alleviated by discontinuation of heparin. If extracorporeal mechanical circulatory support is needed, alternative anticoagulation must be used. Argatroban (GlaxoSmithKline, Philadelphia, PA), a direct thrombin inhibitor, has been used successfully in CPB for adults (2,3) and in neonatal (4) and adult (5) extracorpo-

real membrane oxygenation (ECMO). Currently, there are no published methods and techniques on the use of argatroban for CPB in the pediatric population.

## DESCRIPTION

A 6-kg female patient who previously underwent a Damus-Kaye-Stansel and a right modified Blalock-Taussig (B-T) shunt procedure in the neonatal period was admitted to the hospital with hypoxia at 3 months of age. The patient underwent a cardiac echocardiogram that showed possible shunt thrombosis. Platelet counts were 41,000/ $\mu$ L at the time and 23,000/ $\mu$ L 6 hours later. A functional HIT assay was performed and came back negative. Arterial saturations dropped from the mid sixties to the twenties which facilitated intubation. The patient underwent cardiac catheterization, which showed a large thrombus in her left pulmonary artery extending across the main pulmonary artery into the B-T shunt. Tissue plasminogen activator therapy was initiated but discontinued after 1-2 hours when the patient clinically deteriorated and was emergently placed on ECMO support. A 10-French non-coated arterial cannula (Medtronic, Minneapolis, MN) was inserted into the right common carotid artery and a 12-French noncoated venous cannula (Medtronic) was placed in the right internal jugular vein.

Our ECMO circuit consists of a HL-20 roller pump

Address correspondence to: Brian Mejak, BS, CCP, Pediatric Perfusion, Doernbecher Children's Hospital, Oregon Health & Science University, DCH8S, 3181 SW Sam Jackson Park Road, Portland, OR 97006. E-mail mejakb@ohsu.edu

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(Jostra, Hirrlingen, Germany) with interfaced pressure transducing, a Medtronic silicone bladder, a Medtronic 800 silicone oxygenator, Conducer heat exchanger (Terumo Cardiovascular, Ann Arbor, MI), a venous saturation cuvette, and an arterial blood gas cuvette (Terumo). No surface coatings were present on any part of the ECMO circuit. The circuit was primed with 600 mL of packed red blood cells, 100 mL of fresh-frozen plasma (FFP), 200 units of heparin, 35 mEq of sodium bicarbonate, and 200 mg of calcium gluconate. Activated clotting times (ACTs) on ECMO initially were adequate (protocol: 180–220 seconds) but then 4 hours later dropped to 121–165 seconds despite elevated heparin infusion rates (50 units/kg/h), the addition of FFP, and the administration of 40 units/kg of antithrombin III concentrate (Bayer Pharmaceuticals, West Haven, CT). Heparin was discontinued and argatroban anticoagulant therapy was instituted as the result of severe heparin resistance and possible presence of HIT. An ACT range of 180–220 seconds was obtained by an initial argatroban bolus of 50  $\mu\text{g}$  and continuous infusion of 2  $\mu\text{g}/\text{kg}/\text{min}$ .

The patient remained on ECMO through the night, with ACTs ranging from 192 to 225 seconds, and was taken to surgery the next day and placed on CPB for pulmonary artery thrombo-embolctomy. The CPB circuit consisted of a BabyRx oxygenator with Xcoating (Terumo, Ann Arbor, MI), 3/16-inch arterial and quarter-inch venous Smart coated tubing (Cobe Cardiovascular, Arvada, CO), and a CXAF02 arterial line filter (Terumo). The circuit was primed with 200 mL of normosol, 50 mL of 25% albumin, 20 mEq sodium bicarbonate, 16 mg of Decadron, 150 mL of red blood cells, and 100 mL of FFP. Seventy-

five micrograms of argatroban was placed in the priming solution before the addition of FFP and red blood cells. The prime solution was passed through a hemoconcentrator (Cobe Cardiovascular) to improve hematocrit levels.

An initial bolus of 600  $\mu\text{g}$  (100  $\mu\text{g}/\text{kg}$ ) and a maintenance infusion rate of 12  $\mu\text{g}/\text{kg}/\text{min}$  of argatroban resulted in an ACT of 306 seconds. A subsequent bolus of 600  $\mu\text{g}$  was administered and the infusion rate was increased to 14  $\mu\text{g}/\text{kg}/\text{min}$ . The resulting ACT was 385 seconds. A final bolus of 300  $\mu\text{g}$  (50  $\mu\text{g}/\text{kg}$ ) was given and an ACT of 400 seconds resulted. The ECMO circuit was clamped off and CPB commenced using the same cannulas from ECMO. The duration of bypass was 231 minutes. Surgeons retrieved a 2-mm clot from the left pulmonary artery and replaced the B-T shunt.

The argatroban infusion rate and resultant ACTs during the case are shown in Figure 1. The argatroban infusion was turned off 69 minutes before the termination of bypass because of elevated ACTs. Thirty minutes after termination of CPB, coagulation parameters were: INR 12.5, PTT >200 seconds, fibrinogen 90 mg/dL, hematocrit 37%, and platelets 73,000/ $\mu\text{L}$ . During the 90 minutes after termination of CPB, 150 mL of red blood cells, 100 mL of FFP, 80 mL of platelets, and 80 mL of cryoprecipitate were administered. After the administration of these products, the following coagulation panel was obtained: INR 5.17, PTT 117 seconds, fibrinogen 237 mg/dL, hematocrit 34%, and platelets 160,000/ $\mu\text{L}$ . Over next 24 hours, the only transfusion necessary was 120 mL of platelets. HIT assays were negative and therefore ruled out as the pathology of the thrombus in the pulmonary artery. Heparin was therapeutically reinitiated to prevent rethrombo-

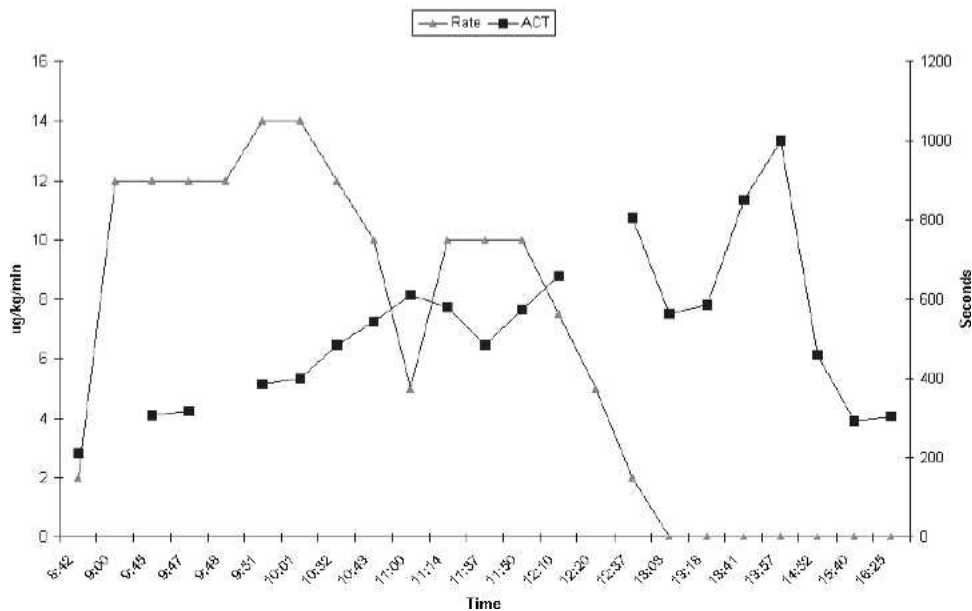


Figure 1. ACT and argatroban infusion rate.

sis of the new B-T shunt. One week later, the patient received a successful cavopulmonary shunt and was later released from the hospital with no complications.

## DISCUSSION

In addition to HIT, patients may exhibit a sensitivity or resistance to heparin. Causes of heparin resistance include antithrombin III deficiency, vascular thrombus formation, preoperative heparin therapy, and endocarditis. We initiated argatroban therapy on the premise of suspected HIT even though the initial HIT assay was negative. Our center has reported negative functional HIT assays up to 3 days before a positive test (4). In this patient, the heparin resistance observed on ECMO was probably caused by the presence of thrombus in the pulmonary artery. The use of argatroban was based on the patient's unresponsiveness to high heparin infusion rates (50 units/kg/min), and low resultant ACTs (120 seconds) after the administration of antithrombin III concentrate and FFP. If HIT can be ruled out, another option to combat heparin resistance would be to run a low-level argatroban infusion (0.12–0.25  $\mu\text{g}/\text{kg}/\text{min}$ ) in combination with heparin, which has been shown to alleviate heparin resistance by raising ACTs *in vitro* (6).

Argatroban is a direct thrombin inhibitor with a half-life of 39–51 minutes and is metabolized in the liver. It is approved by the FDA for both prophylactic use and treatment of thrombosis associated with HIT. Argatroban is superior to heparin in decreasing thrombin generation (7). However, the clear disadvantage to its usage is the lack of a reversal agent. Argatroban should only be used when heparin is contraindicated. We observed small fibrin strands on the reservoir housing after two hours of bypass despite adequate ACTs. Also, when the ECMO circuit was disconnected from the patient, the arterial and venous ends were reconnected and the blood was recirculated at a flow rate of 125–200 mL/min. The oxygenator (Medtronic 800) clotted off despite a circuit ACT of 627 seconds. With this in mind, after separation from bypass, the recirculation rate of the bypass circuit was run at 400–500 mL/min to maintain patency of the circuit and hollow fiber membrane.

There is currently no literature on the use of argatroban in the pediatric population. The unavailability of a reversal agent in combination with the complex nature of pediatric surgery can result in massive blood loss post op-

eratively despite an aggressive correction of coagulation parameters. We suggest frequent ACT testing and adjustments to the argatroban rate to maintain ACTs from 400–500 seconds. We bolused with only 100  $\mu\text{g}/\text{kg}$  initially because the patient was partially anticoagulated for ECMO. We suggest a bolus of 250  $\mu\text{g}/\text{kg}$  and initial infusion rate of 7.5  $\mu\text{g}/\text{kg}/\text{min}$  on a nonanticoagulated patient 30 minutes before bypass. This protocol was derived from our own experience with argatroban as well as other reports in the literature (2,8). Also, the high-dose thrombin Time (HiTT, Hemochron: ITC, Edison, NJ) is another point-of-care option for monitoring the adequacy of argatroban anticoagulation. The benefit of the HiTT test is that it monitors thrombin activity directly and demonstrates effective anticoagulation above levels of 400 seconds (2). In conclusion, argatroban can be used successfully for anticoagulation in the presence of HIT but heparin still remains the gold standard because of its reversibility by protamine.

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