A case of inadvertent overdose with argatroban in a 13-month old toddler in the cardiac catheterization lab setting

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ABSTRACT

A case-report is presented of a toddler who received an overdose of argatroban in the cardiac catheterization lab setting due to suspected heparin induced thrombocytopenia. This is the highest known overdose of argatroban in terms of dose-to-weight ratio. The overdose was treated and the patient was recovered in the intensive care unit. Two other adult case reports are discussed and key lessons and suggestions to improve safety for argatroban and for heparin induced thrombocytopenia patients in the hospital setting are also presented.

Key words: argatroban, overdose, heparin induced thrombocytopenia, safety.

Introduction

Heparin induced thrombocytopenia (HIT) is a complex clinicopathologic syndrome that occurs when autoantibodies are formed and activate platelets, resulting in serious thromboembolic complications including pulmonary embolism, ischemic limb necrosis, and stroke.[1-5] Because HIT has a high risk of thrombosis and can be both life and limb-threatening, alternative anticoagulation is required with current options including fondaparinux, bivalirudin, argatroban and direct oral anticoagulants.[2-4,6]

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Ethical approval: this article does not contain any studies with human participants or animals performed by the author. The case report depicts true care in a hospital setting and subsequent quality improvement strategies.

Informed consent: written informed consent was obtained from the parents of the patient for the case-report and any accompanying information.

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Argatroban suggested dosing, monitoring, and hospital protocolization

Dosing per Lexicomp and "The Teddy Bear Book of Pediatric Injectable Drugs 12th Edition" suggest 0.75 mcg/kg/min initially via continuous intravenous infusion, followed by titration in increments of 0.1-0.25 mcg/kg/min with activated Partial Thromboplastin Time (aPTT) monitoring for prophylaxis or treatment of thrombosis in suspected or confirmed HIT in pediatric patients.[7,8] For non-procedural settings, aPTT should be checked at baseline and 2 hours after initiation with dose adjustments in increments of 0.1 to 0.25 mcg/kg/min to achieve a target aPTT of 1.5 to 3 times the baseline value, not to exceed 100 seconds. Infusion rates have typically ranged from 0.1 to 13 mcg/kg/min in pediatric patients.[8-10]

In the cardiac catheterization setting, a bolus of 150 to 250 mcg/kg and an initial infusion rate of 7.5 to 15 mcg/kg/min is titrated to an activated clotting time (ACT) of 200-300 seconds.[8,9] ACT should be evaluated within 5-10 minutes after each bolus, after any infusion dose rate change, and at 1-hour intervals for cardiac catheterization settings. For adult patients with moderate or severe hepatic dysfunction (*i.e.* Child-Pugh B or C), there is an approximate 4-fold decrease in argatroban clearance as compared to normal hepatic function; thus, it can be anticipated that pediatric patients with liver dysfunction would also have decreased argatroban clearance.[8,9] The US package insert notes that safety and efficacy have not yet been established in pediatric patients but reports that argatroban clearance in seriously ill pediatric patients is approximately 50% of healthy adult patients.[9]

It should be noted that in the US, argatroban is typically monitored by aPTT when patients are on hospital wards while in the operating room or procedural settings, ACT is typically used because of more rapid, in-room turn-around times.[10] Last, experts recommend the development of system level protocols, tools, and interventions to improve the knowledge and expertise of providers and to support delivery of consistent, high-quality, evidence-based care across health systems for patients with suspected or confirmed HIT.[4]

Case Report

Presented here is a case of argatroban overdose in a 13-month old female toddler. Her history included complicated congenital heart disease, cardiopulmonary shock requiring resuscitation, pulmonary stenosis, hypoplastic right ventricle and patent foramen ovale, patent ductus arteriosus ligation, Blalock-Taussig shunt with shunt thrombosis requiring warfarin therapy. She also had multiple Emergency Department (ED) visits for elevated International Normalized Ratio (INR) secondary to warfarin exacerbated by multiple infections and antibiotic use that interacted with warfarin causing high INRs. Her primary medications were warfarin 2 mg by mouth nightly and aspirin 20 mg by mouth daily; however, warfarin was on hold because of the aforementioned high INRs and missed physician appointments at the time of argatroban overdose.

The patient re-presented to the ED at 12 months of life, weighing 7.8 kg, with a chief complaint of blue spells and decreased oxygenation. She was immediately brought to the cardiac catheterization vascular lab (CVL) for a diagnostic catheterization and subsequently experienced a pulmonary hypertensive crisis after administration of sevoflurane for anesthesia induction. She became hypotensive with cold and mottled appearance and endotracheal CO_2 dropped to 6 mmHg; thus, ketamine and atropine were administered, and she was intubated. The patient was anticoagulated with heparin to be adjusted by ACT and fluid resuscitated with Lactated Ringers. Because of noted low hemoglobin of 6.5, a blood transfusion was initiated. However, the transfusion was stopped due to fever and suspicion of a transfusion reaction. During the catheterization, the patient was found to have moderate pulmonary hypertension with low systemic pulmonary arterial pressures, and decreased flow in the left pulmonary artery. The right ventricle was poorly compliant with moderate tricuspid regurgitation, dilated right atrium, and congested liver.

Due to a thrombus noted in the femoral catheter, poor lower extremity perfusion, low platelets, and suspected additional thromboses, the pediatric cardiologist raised concern for HIT that may be presenting during the catheterization. The cardiologist discontinued all heparin products and ordered an immediate argatroban drip. The triaging pharmacist received a scanned order along with a telephone call from the CVL and because there was no standardized pediatric argatroban protocol, the pharmacist utilized the adult size and strength of 250 mg/250 mL at the recommendation of the pediatric pharmacist specialist. The drip was compounded rapidly and the pharmacist physically delivered the medication to the CVL to emphasize the high-risk nature of argatroban and to clarify initial bolus and subsequent dosing with the anesthesiologist. Via a face-to-face encounter with the anesthesiologist, the pharmacist also recommended the bolus and infusion be withdrawn in syringes and a pediatric syringe pump should be utilized. The anesthesiologist and a CVL technician subsequently hung the drip and programmed the pump. Approximately 45 minutes after initiation, the first ACT result was supratherapeutic >450 seconds which prompted clinicians to recognize the drip was infusing at a higher rate than intended. The team realized there had not been a second independent check on the pump and pump rate (*i.e*. the anesthesiologist and tech verified this together at the same time as opposed to separately). After the error was recognized, the drip was immediately stopped, the procedure was completed, and the patient required extended recovery time in the CVL for femoral manual compression.

At her admission weight of 7.8 kg, the patient should have received a bolus between 1.17 to 1.95 mg (1.17 to 1.95 mL of a 1 mg/mL IV solution) followed by an infusion of 3.51 mg (3.5 mL of a 1 mg/mL solution) to 7.02 mg (7 mL of a 1 mg/mL solution) per hour. Due to the manual pump programming error, she received between 70-80 mg of argatroban over less than 60 minutes representing an overdose between 61 to 75.3 mg of argatroban. With her suggested total dose in the first hour being between 4.68 to 8.97 mg, this represents an approximate 7- to 16-fold overdose. Anesthesia noted that the programming error resulted in a 10-fold higher dose/rate than intended.

Due to prolonged elevated ACTs >400 seconds, hemostasis from the sheath removal took approximately 4-5 hours. She was given 200 mL of fresh frozen plasma, sodium bicarbonate IV infusion for metabolic acidosis and inhaled nitric oxide at 20 parts per million for pulmonary arterial hypertension. The patient was transferred to the Pediatric Intensive Care Unit for further recovery and monitoring after hemostasis was achieved.

Initial aPTT's on the ward were greater than 200 and then decreased to 113 after 2 hours, 71 at 5 hours, 55 at 9 hours, 41 at 12 hours, and finally dropped into reference range of 36 at 20 hours. Levels normalized approximately 24 hours after the overdose despite argatroban's short terminal elimination half-life of 39-51 minutes which may be extended to 181 minutes in individuals with liver dysfunction.[9] Because the patient had some liver congestion from her cardiac issues and slightly elevated LFT's prior to admission, the half-life was likely extended. Additionally, her hepatic system may have been overwhelmed with clearing the large dose. Sildenafil was started for her pulmonary hypertension, famotidine for gastrointestinal prophylaxis at admission and cefazolin was administered peri-procedurally for surgical prophylaxis, but none of these medications interact with argatroban's clearance. The overdose did not appear to cause further acute bleeding initially or within the following days after admission.

On the ward, the patient later had a witnessed cardiac arrest which progressed to coma and significant negative neurologic findings with intracranial hemorrhage being suspected initially. The following day, she had an abnormal electroencephalography (EEG) furthering concern for her neurological status. Follow-up head computed tomography showed no evidence of hemorrhage and pediatric intensivists restarted argatroban for bilateral arterial femoral thromboses and the newly resulted HIT antibody of 1.61 (reference less than 0.8) that had been ordered several days prior. The patient remained critically-ill on ventilator support with poor lower extremity perfusion and repeat EEGs demonstrated abnormal results consistent with severe encephalopathy with no epileptiform activity and severe anoxic brain injury post-arrest. After a conference with the care team, the parents decided to not further intervene. Comfort measures were initiated and the patient was terminally extubated 20 days after admission with the patient passing away the following day.

Discussion

Argatroban is a direct thrombin inhibitor indicated for treatment or prophylaxis of thrombosis in HIT or for

percutaneous coronary intervention in adult patients with confirmed or suspected HIT.[9] It is metabolized through the liver and requires dose adjustment in hepatic impairment due to the decrease in hepatic clearance of the drug.[8,9] Argatroban carries a warning for hemorrhage, and with no direct antidote available, thus the drug can be dangerous in overdose and is considered high-risk and complications are more likely to occur with supratherapeutic aPTT values.[6,8-10] The major adverse event with argatroban in humans is hemorrhage [9] while in laboratory models, high doses of argatroban can result in neurological defects including paralysis, coma and death.[11] Data is especially limited in pediatric populations, with no defined goals and duration of treatment, making argatroban difficult to dose and monitor in pediatric patients.

This was a complicated patient with initial 4T score being estimated conservatively as low-probability at 2-3 points for the degree of thrombocytopenia (1 point) and new thrombosis (2 points).[3-5] With a more generous clinical approach, the 4T score may have been assessed as intermediate probability given the remote possibility of heparin exposure within the prior 30-100 days (1 point) and possible "other causes of thrombocytopenia (1 point) for a total 4T score of 4-5. Differential diagnoses of suspected HIT patients may include sepsis, disseminated intravascular coagulation, drug-induced thrombocytopenia, transfusion reactions, immune thrombocytopenia, thrombotic thrombocytopenic purpura, or consumption of platelets due to multiple thromboses.[12,13] The patient was believed to be followed solely by our health system for both the hospital and ambulatory settings and documented prior heparin exposure was well beyond the prior 100 days. However, the interventional cardiologist had a primary clinical suspicion of rapid-onset HIT while conducting a complicated cardiac procedure with a 4T score potentially demonstrating intermediate probability suggesting that this was an appropriate medical decision at the time. Enzyme-linked immunosorbent HIT antibody results had been negative in three prior separate tests. While the last HIT antibody resulted as positive as noted above, no functional assay, such as the serotonin release assay, was ordered despite being available and discussed with pediatric intensivists. Thus overall, the patient had suspected HIT but never had confirmed HIT. No clinician assessed the overdose as having deleterious effects on the patient's overall clinical status or final disposition especially in light of her initial recovery after the overdose. The patient had a complicated cardiac history and likely was already following an unfortunate futile clinical course.

Two separate adult argatroban overdoses have been reported in the literature.[11,14] On postoperative day 24, a 74-year-old male accidentally received argatroban 125 mg over 1 hour (26 μg/kg/min) but had successful recovery with treatment of fresh frozen plasma. [14] In addition, a 65-year-old male with ischemic and valvular heart disease who underwent a successful mitral valve repair when on post-operative day 27, the patient inadvertently received a large intravenous bolus of argatroban over a 1-hr period (~225 mg; ~3.6 mg/kg) and he also successfully recovered. Thus, all three case-reports of argatroban overdose appear to have initially recovered.

Although not addressing argatroban overdose or toxicity specifically, a case-series reported upon the difficulty of argatroban use in critically ill patients,[15] while a separate case-report of a 6-year old with prior HIT noted difficult intraoperative management of argatroban throughout heart transplantation with circuit thrombus formation during cardiopulmonary bypass and subsequent massive hemorrhage after bypass.[16] Thus, there is limited data on argatroban overdose prevention and safety, especially in pediatric patients, and this case report demonstrates the first pediatric patient receiving an argatroban overdose. No specific argatroban antidote exists and overdose treatment consists of discontinuing therapy, supportive care given argatroban's short half-life, monitoring of coagulation parameters such as aPTT, and fresh frozen plasma or other blood product transfusions if clinically necessary.[9,10,17]

Opportunities to avoid inadvertent overdoses include:

- Prioritize and utilize separate, independent pump checks on argatroban drips to minimize risk of error. Although this was current policy at the hospital, deviations occurred due to the urgency of the situation.
- Implement protocols for both pediatric and adult argatroban or bivalirudin drips in the procedural and ward settings.
- Implement a standardized pediatric strength and size. Minimizing syringe/drip size reduces potential total dose by limiting amount of drug if there is an inadvertent administration.
- Use of smart pump infusion technology and alerts which have improved anticoagulation safety.[18]
- Early notification of suspected HIT to pharmacy and anesthesia to allow time to determine the possible need for alternate anticoagulation.
- Being vigilant to not over-suspect HIT and have a good understanding of the complex clinico-pathologic syndrome. Many clinicians do not have a good understanding of HIT.[1]
- Conduct a pretest probability test, such as the 4T score, prior to sending HIT diagnostic lab tests, to evaluate whether the patient is low, intermediate or high risk of HIT.[2,4]

Conclusions

Argatroban is a high-risk anticoagulant that is used in multiple settings and patient safety should be optimized as with other anticoagulants. Limited data on argatroban overdose prevention and safety exist, especially in the pediatric population. After this case occurred, protocols were implemented for pediatric specific populations including on hospital floors and in procedural and surgical settings with well-defined smart-pump guidance on bolus and maintenance dosing. In addition, reduced dose and volume options were standardized to better meet pediatric needs and adult protocols were implemented for procedural settings as a protocol for adult argatroban use on the hospital floor was already implemented. Finally, 4T scoring was mandated prior to HIT laboratory tests or alternate anticoagulation order approval which improved the quality, safety and clinician knowledge for HIT in the hospital setting and greatly reduced over-suspecting of HIT.

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