Journal of Clinical & Experimental Cardiology

Hofer et al., J Clin Exp Cardiolog 2015, 6:11
DOI: 10.4172/2155-9880.1000408

Commentary Open Access

Argatroban as an Alternative Anticoagulant in the Case of Heparin-Induced Thrombocytopenia after Pediatric Cardiac Surgery

Anna Hofer[1*], Martina Heschl[1], Gabriele Leitner-Peneder[2] and Jens Meier[1]

[1]*Department of Anesthesiology and Intensive Care, Kepler Universitätsklinikum Linz, Austria*

[2]*Department of Pediatric Cardiology, Kepler Universitätsklinikum Linz, Austria*

[*]**Corresponding author:** Anna Hofer, Department of Anesthesiology and Intensive Care, General Hospital Linz, Austria, Tel: +43-732-7806-2158; E-mail: anna.hofer@akh.linz.at

Received date: Oct 15, 2015; **Accepted date:** Nov 19, 2015; **Published date:** Nov 22, 2015

Abstract

Heparin-induced thrombocytopenia (HIT) represents a major challenge in patients following the fenestrated Fontan procedure. These patients are prone to thrombosis within the Fontan tunnel due to the low blood flow velocity. The communication between the Fontan tunnel and the common atrium may enable systemic embolization and can cause a stroke. Effective on-going anticoagulation is necessary. Given the high risk of arterial and venous thrombosis with HIT, alternate anticoagulation management is essential as soon as HIT is suspected.

We are reporting on two patients who developed HIT antibodies and thrombocytopenia after exposure to heparin during a Fontan procedure. Both the PF4 enzyme-linked immunosorbent assay (LIFECODES® PF4 IgG assay) and the heparin-induced platelet aggregation test (HIPA, Institut für Immunologie und Transfusionsmedizin, Greifswald, Germany) were positive. The children were treated with argatroban (Argatra®, Mitsubishi Pharma), a direct thrombin inhibitor. In only one patient was HIT associated with thrombosis within the Fontan tunnel.

Keywords: Heparin-induced thrombocytopenia; Fontan; Argatroban; Direct thrombin inhibitor; Pediatric cardiac surgery

Introduction

Heparin-induced thrombocytopenia (HIT) with impending thromboembolic complications presents a major challenge in Fontan patients, especially with the fenestrated Fontan. These patients are particularly prone to thrombosis within the Fontan tunnel due to the low blood flow velocity. In addition, the communication between the Fontan tunnel and the common atrium may become a passageway for systemic embolization and may cause a stroke. Effective on-going anticoagulation without interruption is necessary in every Fontan patient. Given the high risk of arterial and venous thrombosis of HIT, alternate anticoagulation management is essential as soon as HIT is suspected.

The appearance of anti-heparin/PF4 antibodies in childhood is lower than in adult patients. The reason for this may be the immature immune system and lower platelet Factor 4 (PF4) levels [1]. However, after cardiac bypass surgery the number of children developing antibodies is similar to that of adults. Antibody formation has been reported to be 1.7% in neonates and 16% in children after re-operative cardiac surgery on the 5th postoperative day. On the tenth postoperative day even 52% of re-operated children were antibody positive (ELISA) but only 1.3% developed symptoms like thrombosis or skin lesions [2].

We are reporting on two patients who developed HIT antibodies and thrombocytopenia after re-exposure to heparin during a Fontan procedure.

Patient 1	
Diagnosis	DORV/Criss-cross heart, TGA, Pulmonary atresia, Hypoplastic right ventricle, VSD
Nov. 2009	Cardiac Catheterization
Nov. 2009	Norwood/Sano
Feb. 2010	Cardiac Catheterization
Feb. 2010	Bidirectional Glenn
Nov. 2010	Cardiac Catheterization
Nov. 2010	Fenestrated Fortan, Lateral Tunnel
Patient 2	
Diagnosis	Hypoplastic left heart syndrome, Mitral and Aortic atresia
July. 2008	Norwood/Sano
Nov. 2008	Sano conduit change
Nov. 2008	ECMO/RSV infection
Mar. 2009	Cardiac Catheterization
Mar. 2008	Bidirectional Glenn
Oct. 2012	Cardiac Catheterization
Oct. 2012	Fenestrated Fortan, Lateral Tunnel

Table 1: Diagnosis and heparin exposure during diagnostic and surgical procedures.

The first patient, a three-year-old boy had undergone stage one and two palliation for a complex cardiac malformation with a hypo plastic right ventricle. He also had a cardiac catheterization before every surgical step including the preoperative evaluation before the Fontan procedure (Table 1). A fenestrated lateral tunnel was generated on cardiopulmonary bypass and unfractionated heparin (UFH) was administered to maintain an activated clotting time (ACT) above 480 seconds. In the intensive care unit (ICU) heparin was infused continuously with the intention of keeping the activated partial thromboplastin time (aPTT) at about 60 seconds.

Before surgery the platelet count had been within the normal range. Because of excessive bleeding and thrombocytopenia at the end of the procedure, one unit of platelets was transfused. After an initial recovery to 109 G/l, the platelet count dropped again to a minimum of 31 G/l on the sixth postoperative day. According to the 4T scoring system there was a high risk for ongoing HIT [3]. Heparin was stopped immediately and anticoagulation was continued by a continuous infusion of the direct thrombin inhibitor argatroban. The dosage needed to achieve the targeted aPTT of about 60 seconds varied between 2 and 6.1 µg/kg/min (Table 2).

Five days after the initiation of argatroban the platelets recovered without supplementation. According to our routine management after the Fontan procedure, a Vitamin K antagonist (phenprocoumon, marcoumar®) was started as soon as the chest tubes had been removed on the 12th postoperative day. Argatroban was continued until the International Normalized Ratio (INR) reached 3.9. This rather high value was accepted because argatroban is known to induce elevated INR values *in vitro* with the Quick-type measurement currently used at our institution.

No thrombotic event occurred in this patient, especially no thrombus formation within the Fontan tunnel was observed.

The second patient, a four-year-old girl with hypoplastic left heart syndrome underwent a Norwood procedure at the age of two weeks. At the age of four months she had a replacement of her 5 mm Sano shunt with a 6 mm shunt. She needed ECMO therapy after the operation due to respiratory failure caused by a respiratory syncytial virus infection. After recovery a Glenn anastomosis was performed at the age of eight months. Altogether she was exposed to UFH during three surgeries, one ECMO, and two cathetherization procedures and her right femoral vein had been found occluded before the Fontan procedure (Table 1).

The Fontan operation was performed without complications. The girl received UFH again during cardiopulmonary bypass and according to our routine clinical care as a continuous infusion in the ICU. After an uneventful postoperative course, the platelet count decreased from a postoperative value of 127 G/l to 48 G/l on the 7th postoperative day. Heparin was stopped immediately after thrombocytopenia had been detected and argatroban was started (1 µg/kg/min to a maximum dosage of 7.078 µg/kg/min). The platelet count returned to normal within four days. After the chest drain was removed on day ten after surgery the child was in respiratory distress and needed urgent intubation. At that time a thrombus was suspected within the Fontan tunnel using transthoracic echocardiography (TTE) and confirmed by transoesophageal echocardiography (TEE).

Date	Time	Argatroban µg/kg/min	Platelet count G/l	aPTT	Phenprocoumon (mg)	INR
14.11.12	18:00	2	31	51	-	-
14.11.12	21:00	2.5	-	44	-	-
15.11.12	0.:30	3	-	45	-	-
15.11.12	3:00	4	-	47	-	-
15.11.12	9:00	4.5	55	48	-	-
16.11.12	9:30	5	75	53	-	-
16.11.12	12:30	5.1	-	59	-	-
17.11.12	14:00	5.5	105	58	-	-
17.11.12	16:45	6.1	-	48	-	-
18.11.12	6:09	5.5	-	81	-	-
18.11.12	12:30	5.5	-	64	-	-
19.11.12	8:05	5.5	198	70	3	-
20.11.12	8:52	5.5	-	-	2	1.4
21.11.12	8:15	5.5	-	-	1.5	2.7
22.11.12	-	ex	-	-	1.7	3.9
23.11.12	7:52	-	-	-	1	3.4

Table 2: Time intervals for argatroban dosage, platelet count, aPTT and transition to phenprocoumon in patient 1.

Argatroban was continued until an aPTT of 70 seconds was reached. Phenprocoumon was stopped because of recurrent pleural effusions, which required drainage and argatroban was continued until the chest drain was removed. After that, phenprocoumon was restarted. Initially, during four days of dual therapy, the aPTT and INR were in the therapeutic range. On the fifth day the aPTT was suddenly over therapeutic levels. Argatroban was withheld for 10 hours. Phenproucoumon was continued because INR had supposedly not reached [4]. A retrospective chart review however revealed a change in the INR measurement method using a point-of-care test (CoaguCheck, Roche Diagnostics®). The concomitantly measured Quick-type INR values (Table 3) were much higher, but the target of capillary whole blood measurements was erroneously considered the same as that of the Quick-type measurement values. Despite the resulting high aPTT no bleeding was observed.

A TTE three weeks later showed no more thrombi in the Fontan tunnel and an open fenestration.

Discussion

These two patients were among a high-risk population for HIT, since repeated exposure to UFH had been necessary for diagnostic and surgical procedures. The formation of anti-heparin/PF4 antibodies has been associated with the total number of previous UFH exposures and with patient's age during surgery [1]. Both of our patients had cardiac catheterization prior to their Fontan procedure and developed thrombocytopenia on the sixth and seventh postoperative day respectively. According to the 4T scoring system for suspected HIT a high probability was stated and UFH was discontinued [3].

Date	Time	Argatroban (µg/kg/min)	Platelet count G/l	aPTT	Phenprocoumon (mg)	INR
8.11.12	7:47	1	58	35	-	-
8.11.12	21:38	1.9	48	50	-	-
9.11.12	0:17	2.36	-	47	-	-
10.11.12	9:30	2.36	120	58	-	-
11.11.12	8:25	2.95	161	58	-	-
11.11.12	21:39	3.3	-	-	3	1.9
12.11.12	15:20	2.95	205	71	pause	2.24
13.11.12	9:02	2.95	313	71	0.75	2.9
14.11.12	9:32	2.59	-	81	0.75	3.1
17.11.12	9:25	2.71	459	70	0.75	2.98
18.11.12	8:08	2.95	460	58	pause	2.56
18.11.12	22:35	4.01	-	61	pause	2.52
19.11.12	11:00	5.3	-	69	pause	3.12
20.11.12	9:00	7.08	470	54	pause	2.47
21.11.12	7:53	3.54	-	73	pause	3.15
23.11.12	16:00	4.13	-	66	pause	2.74
25.11.12	8:30	4.13	-	67	3	2.62
26.11.12	7:00	4.13	528	70	2	2.74
27.11.12	8:00	4.13	489	84	1	3.66/1.7*
28.11.12	10:00	4.13	-	88	2	4.6/2.4*
29.11.12	11:00	pause	-	240	2	6.56/3.1*
29.11.12	12:00	pause	-	74	-	-
29.11.12	17:00	pause	-	106	-	-
29.11.12	20:50	2.36	-	50	-	-
30.11.12	3:12	ex	-	99	1.5	3.9*

Table 3: Time intervals for argatroban dosage, platelet count, aPTT, and transition to phenprocoumon in patient 2; *CoaguChek® measurements.

Clinical assessment concerning time and extent of thrombocytopenia as well as occurrence of thrombosis resulted in 6 and 8 points respectively. A sudden drop in the thrombocyte count within 6 and 7 days was observed, the lowest value did not fall below 31 and 48G/l, there was thrombosis verified by echocardiography in one patient, and thrombocytopenia was not due to other reasons like sepsis or drug induced thrombocytopenia in either patient. As soon as 4-5 points of the score are reached laboratory testing is strongly recommended. An IgG specific Elisa test was performed at our hospital and simultaneously a blood sample was sent to the reference laboratory to perform a functional test because only a minority of anti-PF4/Heparin antibodies can activate platelets, cause platelet aggregation and thrombosis. Antibody formation was detected by the ELISA test and confirmed by the functional HIPA test. After discontinuation of UFH platelet counts returned to normal within five and four days respectively. The thrombus detected in one patient within the Fontan tunnel close to the fenestration fortunately did not cause cerebral or additional systemic embolization.

We decided to use argatroban as an alternate anticoagulation. By binding to the catalytic site of thrombin, argatroban inhibits the action of thrombin, such as fibrin generation and platelet aggregation. As a direct thrombin inhibitor (DTI), acting independently of antithrombin, argatroban, in contrast to UFH, it also has the capacity to inhibit thrombin bound to fibrin. In addition, DTIs offer a more predictable response over UFH as they do not bind to plasma proteins. Both the indirectly mediated mechanism of action and the rapid binding to plasma proteins of UFH may cause heparin resistance, i.e. the failure of high doses of heparin to raise the aPTT to target levels. Lepirudin and bivalirudin have been used in pediatric HIT but these drugs are associated with a high rate of antibody formation [4]. According to an open-label safety and efficacy study in 18 children argatroban 0.75 μg/kg/min (0.2 μg/kg/min with hepatic impairment) is recommended. Major bleeding occurred in two patients.

No problems were caused in our patients from the anticoagulation management with argatroban and the aPTT values were more predictable than with UFH. According to our clinical practice fenestrated Fontan patients anticoaglutation is switched to oral phenprocoumon after removal of chest tubes and continued until three months after closure of the fenestration by catheterization. Thereafter, in the absence of thrombosis patients may receive acetylsalicylic acid only. Unfortunately argatroban has the ability to inaccurately increase Quick-type INR measurements through substantial thrombin inhibition in vitro. Though this is a drug-laboratory phenomenon, it is particularly challenging in the transition to a vitamin K antagonist (VKA). In fact, we had to adjust and even withhold argatroban when we finally moved on to oral anticoagulation in our second patient. According to the manufacturer`s instructions for the Quick-type PT-assay we discontinued argatroban at an INR of about 3.9 in our first patient. Because of paucity of venous access, the INR measurement in our second patient was switched to a point-of-care method using capillary whole blood and it displayed a different result in comparison to the concomitant Quick-type measurements. These different INR values were inadvertently targeted at a higher range and with continued argatroban infusion the aPTT surpassed therapeutic values far more than expected by the impact of VKAs on this clotting assay [5]. In this case, interrupting the argatroban infusion was presumably justified but may bear a risk of thrombosis as long as INR values are not in the therapeutic range. Apart from that a higher dosage of argatroban than recommended for children was required in our patients to reach therapeutic aPTT values [6]. The combined effect of argatroban and vitamin K antagonists on the INR depend on factor depletion by vitamin K antagonism, on test characteristics, and especially on the plasma argatroban concentration. The Owren-type PT assay has been shown to be less influenced by DTIs probably due to the fact that factor V and fibrinogen of bovine plasma are added [7]. Obviously, the effect of argatroban on the point-of-care test used in our second patient was different as well possibly due to the use of whole capillary blood. No gold standard of anticoagulation currently exists due to this variation in the individual response of patients and hence difficulties with monitoring may arise.

Conclusion

Argatroban was used in two children with established HIT without complications. The transition to a vitamin K antagonist is challenging and particular attention must be paid to the interpretation of coagulation assays. Further studies on argatroban as an alternative to heparin anticoagulation after congenital cardiac surgery are needed.

References

1. Takemoto CM, Streiff MB (2011) Heparin-induced thrombocytopenia screening and management in pediatric patients. Hematology Am Soc Hematol Educ Program 2011: 162-169.
2. Mullen MP, Wessel DL, Thomas KC, Gauvreau K, Neufeld EJ, et al. (2008) The incidence and implications of anti-heparin-platelet factor 4 antibody formation in a pediatric cardiac surgical population. Anesth Analg 107: 371-378.
3. Warkentin TE (2003) Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 121: 535-555.
4. Vakil NH, Kanaan AO, Donovan JL (2012) Heparin-induced thrombocytopenia in the pediatric population: a review of current literature. J Pediatr Pharmacol Ther 17: 12-30.
5. Harder S, Graff J, Klinkhardt U, von Hentig N, Walenga JM, et al. (2004) Transition from argatroban to oral anticoagulation with phenprocoumon or acenocoumarol: effects on prothrombin time, activated partial thromboplastin time, and Ecarin Clotting Time. Thromb Haemost 91: 1137-1145.
6. Young G, Boshkov LK, Sullivan JE, Raffini LJ, Cox DS, et al. (2011) Argatroban therapy in pediatric patients requiring nonheparin anticoagulation: an open-label, safety, efficacy, and pharmacokinetic study. Pediatr Blood Cancer 56: 1103-1109.
7. Jackson CM, Esnouf MP (2005) Has the time arrived to replace the quick prothrombin time test for monitoring oral anticoagulant therapy? Clin Chem 51: 483-485.