Subject is reviewed and the relationship between argatroban dosage and activated clotting time

Methods: review the cases previously published in order to better define indications, dosage, monitoring and limitations in cardiac surgery patients.

Pediatric population

A high rate of false positive findings limits the value of the current range of tests, and these are undertaken usually after a precursor event. Among the alternatives to heparin proposed are the direct thrombin inhibitors like desirudin, lepirudin and bivalirudin. Among these undertaken usually after a precursor event. Among the alternatives to heparin proposed are the direct thrombin inhibitors like desirudin, lepirudin and bivalirudin. However, two major drawbacks of this recombinant technology are the need for the ecarin clotting time for monitoring the level of anticoagulation, a method not readily available in all cardiac surgery centers, and the excretion through the renal route, which makes it less attractive in a patient with renal impairment.

Another synthetic direct thrombin inhibitor recently developed is the argatroban that binds reversibly to the thrombin’s site, is eliminated through the hepatobiliary system and can be adequately monitored with the activated clotting time (ACT). Herein, we report a case treated with argatroban during cardiopulmonary bypass (CPB) and review all similar cases published in the literature in order to better define the role of this drug in the surgeon’s and cardiac anesthesiologist’s armamentarium.

2. Material and methods

This article reports a patient with heparin-induced thrombocytopenia and thrombosis (HITT) who underwent mitral valve replacement (MVR) with the use of argatroban during CPB. Moreover, in order to review the literature, a systematic, comprehensive approach was used to identify articles describing argatroban use during CPB. A literature search was performed using the PubMed database, with no temporal or study type limitations applied. The search terms combinations of ‘argatroban’ and ‘cardiovascular procedures’ and ‘cardiopulmonary bypass’ were used.

In addition, the relationship between the varying doses of argatroban and ACT values was studied by analyzing a set of data collected from our experience. Regression analysis was employed and a \( P \leq 0.05 \) was considered significant.
3. Case report

A 63-year-old female was admitted to the cardiology ward with congestive heart failure. The work-up included trans-thoracic echocardiogram and cardiac catheterization, which showed good left ventricular function, severe mitral regurgitation with moderate stenosis and normal coronaries. Because of low platelet count she underwent hematology work-up which revealed type II HITT.

Since the ecarin clotting time was not available to monitor the use of recombinant hirudins, it was decided to employ argatroban during CPB for MVR. Anesthesia was induced with sodium pentothal and maintained with ramifentanyl and propofol. After induction, argatroban was started at 2.5 μg/kg/min and increased until an ACT of 500 was reached. No bolus nor additional dose to the pump prime was given. As a routine, tranexamic acid was given as a bolus (1000 mg) and by intravenous infusion (160 mg/h). The heart was exposed with a minimally invasive approach through a small right anterior thoracotomy. CPB was instituted with direct cannulation of the aorta and femoral venous cannulation of right atrium, the aorta was cross-clamped and crystalloid cardioplegia (Custodiol™) was given. After achieving an ACT of 500 to initiate CPB, the argatroban infusion was titrated to maintain this value with the minimum dosage required in order to avoid postoperative bleeding, as recommended by Martin et al. [4]. The mitral valve was replaced with a mechanical prosthesis (ONX®). The cross-clamp time and CPB time were 83 and 207 min, respectively. Soon after releasing the cross-clamp the oxygenator presented several clots and had to be changed. Change of the oxygenator and circulatory arrest occurred during the delicate phase of myocardial reperfusion: additional pump time was required to properly resuscitate the heart. After weaning from patient CPB the argatroban infusion was stopped. Postoperative bleeding was 770 cc in the first 24 h. Although the patient did not bleed postoperatively, she required transfusion of seven units of red blood cells in order to replace what was lost in the full oxygenator. Additionally, fresh frozen plasma and platelets were given prophylactically, at the end of the procedure, because of the prolonged ACT for a few hours. The values of argatroban infusion rates and the ACTs are plotted against time in Fig. 1. Clotting of the oxygenator occurred with an ACT of 495. The infusion was increased again after the event. Postoperative course was uneventful and the patient was discharged home.

4. Comment

The ideal drug for anticoagulation during CPB should be readily available and characterized by rapid deactivation of the coagulation cascade. In addition, it should be easily monitored by current methods, fully neutralized by an antidote and should have a short half-life. Heparin fulfills all these requirements in all patients with the exception of those who develop HIT/T.

In this subset of patients, despite much emphasis given in the recent literature on this subject, a valid alternative is lacking. Some drugs have been employed on a compassionate basis (ancrod, iloprost) and others off-label (recombinant hirudins, lepirudin) [2]. Currently, given the major role played by thrombin in the pathogenesis of HIT/T, non-cross-reacting direct thrombin inhibitors are the preferred agents. None of them, however, is able to be rapidly reversed, relying on the natural elimination by renal excretion or hepatic metabolism.

4.1. Composition and pharmacokinetics of argatroban

Among other direct thrombin inhibitors, argatroban has been also used off-label because its efficacy in binding to both free and clot-bound thrombin, simple monitoring with the ACT, hepatobiliary excretion and a short half-life of 30 min. Argatroban is a synthetic molecule derived from L-arginine, C23H36N6O5S-H2O. The anticoagulant effect is concentration-dependent, comprises both free and clot-bound thrombin, exhibits no interaction with platelets or heparin antibodies, and has no fibrinolytic or other anti-thrombotic activity other than thrombin inhibition. The molecule binds only to the active site of thrombin, differently from hirudins which interact both with the recognition site and the active center. The compound has a low distribution volume of 180 ml/kg, therefore does not dif-
fus in the tissues but in the extracellular space. About 50% of the drug is protein bound \([5]\). Pharmacokinetic studies \([6]\) in healthy volunteers have shown a close correlation between drug dosage and coagulation test like ACT and activated partial thromboplastin time (APTT).

Since hypothermia is frequently used in cardiac surgery, another attractive feature is represented by the temperature independence of the elimination pathway, differently, for example, from other direct thrombin inhibitors, like bivalirudin, which requires a core temperature of 37 °C for the proteolytic cleavage of approximately 80% of the drug \([4]\). Similarly to the other thrombin inhibitors, though, argatroban does not have a reversal agent and carries the potential for life-threatening postoperative bleeding.

4.2. Review of the literature

Including our report, we have collected 13 cases (Table 1) where argatroban has been used instead of heparin during CPB to undergo cardiac surgery. Interestingly, four are infants, and, to our knowledge, argatroban is the only substitute to heparin employed during CPB in this age group to date. We cannot explain argatroban’s preference in pediatrics, although it could be argued that, after the first report, the others followed just because there was no other experience available.

The protocols varied widely, with the majority starting with a bolus intravenously and a dose in the prime before the infusion while others, including us, going for the infusion only. We believe the loading dose simply shortens the time necessary to reach the target ACT; since it was our first experience we preferred to study the dose response effect of the continuous infusion. The most common loading dose used was 100 µg/kg, while the infusion ranged between 5 and 15 µg/kg/min. In all reports anticoagulation was monitored by ACT, although Edwards et al. \([8]\), in a correct manner, proposed the use of high dose thrombin test because it is thrombin dependent, especially indicated when a direct thrombin inhibitor is substituted to heparin. Overall, everybody started CPB with an ACT of at least 350, preferably above 400, with peak values during CPB up to 1000. With the exception of one case which underwent delayed chest closure, none was returned to the operating room for bleeding. However, judging from the amount of blood products administered and from the prolonged ACTs after termination of argatroban, the patients must have bled intraoperatively, before closure.

From the analysis of the cases published in the literature three observations can be made. First, the long time for the coagulation assays, whether measured with ACT or other tests, to normalize after the infusion of argatroban has been stopped and second, as a result, a significant postoperative bleeding, measured by the amount of blood products given. Thirdly and most disconcerting, the report of clots in the reservoir and in the oxygenator in two cases and the need for replacing it during the CPB time in the case reported above.

With regard to the first two observations, our analysis of the data from our experience showed a relationship between increasing dosage and ACT \((F = 104.034, P = 0.000135)\). However, there was no relationship on decreasing dosage or on discontinuing the argatroban \((F = 1.349417, P = 0.278864)\). In this regard, it is of notice that data obtained in a different experimental protocol with highly specialized pharmacologic modeling on healthy volunteers showed good correlation between decreasing doses and ACT and APTT \([6]\). Furthermore, we should consider that, as alternatives to heparin are often used in patients that have some sort of derangements in their coagulation pattern, drug action could possibly differ from that observed in healthy volunteers.

Undoubtedly, addition of the extracorporeal circuit and the reservoir represents another variable increasing the volume distribution of the drug. In fact, suspension of argatroban coincides with discontinuation of CPB and reinfusion of the argatroban rich remaining blood in the oxygenator, which, in turn, may act as a new bolus dose. Our patient did not bleed postoperatively, despite elevated ACTs because of the minimally invasive approach which offered very little raw surfaces; it might have gone differently had we chosen the traditional midline sternotomy approach.

Equally challenging is to try to explain the finding of clots in the oxygenators of two cases and in ours. One common element is represented by the fact that all three cases were associated with prolonged CPB times raising the likelihood that, with time, the distribution of the drug does not remain constant in the reservoir of the oxygenator. Additionally, in our case, we could identify two factors contributing to the incident. As mentioned above the antifibrinolytic agent tranexamic acid was used and it might indeed have played a deleterious role as a procoagulant. In fact, although during cardiac surgery procedures fibrinolysis may occur as a result of prolonged CPB and as a direct action of heparin, argatroban per se does not seem to have the profibrinolytic potential described for heparin \([17]\). Second, the incident happened when the infusion of argatroban was being decreased (Fig. 1) in order to maintain an ACT around 500 in the fear of postoperative bleeding and it can be postulated that the levels of the drug dropped more in the reservoir than in the patient; perhaps more consideration should have been given to the impact of the pump prime at that stage.

5. Conclusions

The report of clots in the oxygenator during CPB, despite adequate ACTs, on one side and the excessive bleeding postoperatively reported by some authors on the other might signify either the agent is difficult to dose up or the ACT monitoring is inadequate or both. In this respect, Harder et al. have observed a peculiar sensitivity in patients treated with argatroban after cardiac surgery, where CPB anticoagulation was managed conventionally with heparin or with heparin plus tirofiban \([18, 19]\). Interestingly, the initial dose of 0.8–1 µg/kg/min had to be reduced to 0.5 µg/kg/min in order to maintain a target APTT between 60 and 80 s. The authors postulated a transient impairment of liver function after CPB, concluded that a tight monitoring was necessary and that probably other essays, like the ecarin clotting time, should be investigated in this subset of patients. A central question prompted by this study is
<table>
<thead>
<tr>
<th>Author (Ref. no.)</th>
<th>Age/sex</th>
<th>Procedure</th>
<th>ARG in</th>
<th>ARG bolus</th>
<th>ARG infusion (μg/kg/min)</th>
<th>ACT starting CPB</th>
<th>Peak ACT</th>
<th>CPB time</th>
<th>Time to baseline ACT after stopping ARG</th>
<th>Blood products</th>
<th>CTO</th>
<th>Exploration for bleeding</th>
<th>Outcome</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furukawa et al. [7]</td>
<td>44 male</td>
<td>AVR</td>
<td>None</td>
<td>100 μg/kg</td>
<td>5–10</td>
<td>350</td>
<td>400</td>
<td>167</td>
<td>6 h</td>
<td>2 urbc</td>
<td>350 cc in 24 h</td>
<td>No</td>
<td>Good</td>
<td>Report clots in reservoir</td>
</tr>
<tr>
<td>Edwards et al. [8]</td>
<td>68 female</td>
<td>CABG + TVA</td>
<td>50 μg/kg</td>
<td>100 μg/kg × 1</td>
<td>5–10</td>
<td>400</td>
<td>470</td>
<td>97 min</td>
<td>24 h</td>
<td>9 urbc 9 uffp 13 uplt 20 ucryo</td>
<td>3800 cc in 24 h</td>
<td>No</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Kamei et al. [9]</td>
<td>Male</td>
<td>LVAS</td>
<td>None</td>
<td>100–300 μg/kg</td>
<td>5–25</td>
<td>&gt; 400</td>
<td>999</td>
<td>12 h</td>
<td></td>
<td>975 cc</td>
<td>No</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamei et al. [9]</td>
<td>Male</td>
<td>LVAS implantation</td>
<td>None</td>
<td>100–300 μg/kg</td>
<td>5–25</td>
<td>&gt; 400</td>
<td>999</td>
<td>7 h</td>
<td></td>
<td>1197 cc</td>
<td>No</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malherbe et al. [10]</td>
<td>9 months old</td>
<td>Removal of vegetations</td>
<td>None</td>
<td>250 μg/kg × 3</td>
<td></td>
<td>999</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gasparovic et al. [11]</td>
<td>82 male</td>
<td>AVR redo</td>
<td>None</td>
<td>None</td>
<td>10</td>
<td>350</td>
<td>745</td>
<td>169</td>
<td>&gt; 8 h</td>
<td>500 cc rbc 375 cc ffp 2 uplts 26 urbc 24 uffp 60 uplt 7 ucryo 60 cc plt</td>
<td>No</td>
<td>but delayed chest closure</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Dyke et al. [12]</td>
<td>2.5 months old</td>
<td>Excision TV</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>412</td>
<td>462</td>
<td>28’</td>
<td></td>
<td>214</td>
<td>60 cc plt</td>
<td>No</td>
<td>Good</td>
<td>Report clots in oxygenator</td>
</tr>
<tr>
<td>Mejak et al. [13]</td>
<td>3 months old</td>
<td>Thrombectomy</td>
<td>TVA</td>
<td>75 μg</td>
<td>12</td>
<td>400</td>
<td>1000</td>
<td>231’</td>
<td></td>
<td>150 cc rbc 100 cc ffp 80 cc plt 80 cc cryo 20 urbc 18 uffp 30 uplt 5 ucryo 3 urbc 1 ucryo 5 uffp 1 uplt 2 urbc 6 uffp 2 uplt</td>
<td>No</td>
<td>Good</td>
<td>Bleeding complication from femoral artery POD1 DVT on POD3</td>
<td></td>
</tr>
<tr>
<td>Kurup et al. [14]</td>
<td>85 female</td>
<td>AVR + CABG</td>
<td>None</td>
<td>100 μg/kg</td>
<td>5–15</td>
<td>&gt; 400</td>
<td>&gt; 700</td>
<td>127’</td>
<td></td>
<td>185</td>
<td>700 cc in 24 h</td>
<td>No</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Martin et al. [4]</td>
<td>48 male</td>
<td>MVR</td>
<td>None</td>
<td>100 μg/kg/min</td>
<td>3–6</td>
<td>253</td>
<td>753</td>
<td>29 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith et al. [15]</td>
<td>70 male</td>
<td>MVR + CABG</td>
<td>None</td>
<td>4200 μg</td>
<td>350 μg/kg</td>
<td>25</td>
<td>320</td>
<td>476</td>
<td>90’</td>
<td></td>
<td>276</td>
<td>No</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Ciccato et al. [16]</td>
<td>5 days old</td>
<td>Repair DORV + pulmonary stenosis</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>400</td>
<td>1000</td>
<td>179</td>
<td></td>
<td>335 cc rbc 1360 cc ffp 500 cc plt</td>
<td>No</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follis (present report)</td>
<td>66 female</td>
<td>MVR</td>
<td>None</td>
<td>None</td>
<td>2.1–14</td>
<td>495</td>
<td>999</td>
<td>208’</td>
<td></td>
<td>287</td>
<td>770 cc in 24 h</td>
<td>No</td>
<td>Good</td>
<td>Clotted oxygenator</td>
</tr>
</tbody>
</table>

ARG, argatroban; CPB, cardiopulmonary bypass; ACT, activated clotting time; CTO, chest tube output; AVR, aortic valve replacement; urbc, units of red blood cells; CABG, coronary artery bypass; TVA, tricuspid valve anuloplasty; uffp, units of fresh frozen plasma; uplts, units of platelets; ucryo, units of cryoprecipitate; LVAS, left ventricular assist device; redo, reoperation; TV, tricuspid valve; LPA, left pulmonary artery; MVR, mitral valve replacement; DVT, deep vein thrombosis; DORV, double outlet right ventricle.
when the impaired liver clearance of argatroban occurs: if it starts earlier, during the pump run, then it could account for the lack of relationship between cessation of the drug and ACT we have observed. Similarly, it could also explain why in all collected cases, the effects of the drug on the coagulation cascade were prolonged beyond its advertized half-life. Some of these concerns, in fact, have been previously raised and debated by Warkentin and Greinacher [20].

In consideration of the cases reported in literature and of our limited experience, we do not feel that the safety of argatroban has been proven, as an alternative to heparin during CPB, to the point to recommend its liberal use. Further experimental work in the animal model is needed to clarify the issues debated above. As a matter of fact, the American College of Chest Physicians evidence-based clinical practice guidelines [21], recently published, do not list argatroban as a recommended agent in patients with HIT/T undergoing cardiac surgery.

With the current knowledge, its use should be restricted to patients with renal failure, where recombinant hirudin would be contraindicated. Once it is elected, however, we recommend the following strategy:

1. Although heparin is by far not the only cause of hyperfibrinolysis in cardiac surgery and its absence does not protect the patient from it, withholding antifibrinolytic agents should be considered, in view also of the fact that argatroban itself does not activate the fibrinolytic cascade (factor XII, kallikrein and plasmin).
2. Once an ACT between 500 and 600 has been achieved, maintenance of a constant rate of infusion of argatroban until completion of CPB, when the drug can be stopped.
3. Use of low volume prime oxygenator and disposal of blood remaining in the reservoir, rich of argatroban, upon termination of CPB.
4. Select, if possible, a minimally invasive approach like beating heart surgery [22] or minithoracotomy, since the former will decrease the level of anticoagulation required and the need for CPB, while the latter will reduce the raw surface area.

References