Reviewer's report

Title: Lepirudin as an alternative to heparin allergy, during cardiopulmonary bypass

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Reviewer: Dimitrios Angouras

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MAJOR COMPULSORY REVISIONS

1. This is a case report of a patient with heparin allergy who underwent open heart surgery (OHS) for atrial septal defect closure employing a lepirudin based anticoagulation protocol during cardiopulmonary bypass (CPB). The mechanisms of action and several aspects of clinical use of lepirudin (mainly dosage regimens, and anticoagulation monitoring) are discussed. Hirudins (either lepirudin or the more recent bivalirudin) are currently well described alternatives to standard unfractionated heparin for anticoagulation during CPB, with several case reports, a number of large case series, and excellent reviews having already been published in the literature. These direct thrombin inhibitors are typically employed during OHS in patients with heparin induced thrombocytopenia (HIT). The allergy to heparin is indeed an unusual indication for lepirudin utilization. The expansion of indications for hirudin application during CPB in this subset of patients is a sufficient reason to publish this report. To the best of my knowledge there is only one similar case reported few years ago (Pappalardo F et al. Successful use of bivalirudin for cardiopulmonary bypass in a patient with heparin allergy. Perfusion 2007; 22: 67-69). This publication should be included in the reference list and could actually be utilized as a model to guide rewriting of the current case report.

2. The Introduction is too long. The brief review of HIT syndrome (“Heparin-induced thrombocytopenia type II, is an immune-mediated condition… who undergo open heart surgery (7)”) is irrelevant and should, therefore, be excluded. It could be replaced with a brief discussion of the several types of immune-mediated reactions to heparin, including both HIT and the immediate type I hypersensitivity reaction, experienced by the patient of the current case report. This should be included in the Discussion section.

3. The Discussion is also too long. Some information is given, only to be repeated several paragraphs later making the text unnecessarily long and cumbersome to read (e.g. Para. 5: “Many variations in dosage regimes for Lepirudin use with CPB have been described by different authors (4), (11), (12). The most common dosage regime is 0.25-0.4 mg/kg I.V bolus, 0.20 mg/kg in the pump prime and 0.15 mg/kg/hr maintenance dose ...” – Para. 13: “Different dosage regimes have been described for the drug, all involve an initial loading dose, a pump prime dose and a maintenance infusion.” Extensive rewriting
should be undertaken to omit rather unnecessary information that can be found in more extensive reviews (e.g. Introduction - paragraphs 2,3, and 4, or “Each vial of Refludan contains 50 mg of lepirudin”) and focus on practical patient management issues:

As discussed by the author, the safety profile of lepirudin is limited because its half-life is relatively long, elimination is exclusively renal, and “the standard ACT testing… [is] inadequate” to monitor systemic anticoagulation during CPB. Moreover, severe anaphylactic reactions to lepirudin have been reported. In view of the anaphylactic reaction to heparin of this particular patient, a similar reaction to lepirudin was possible. Since the patient had no prior history of lepirudin exposure the possibility was rather remote yet existent as anaphylactic and anaphylactoid reactions on first exposure have been reported (Circulation 2003;108(17):2062-5). On the other hand, the more recent bivalirudin is a reversible direct thrombin inhibitor with a shorter half-life and an elimination which is predominately achieved by proteolytic cleavage and, only to a minor extent, by renal excretion. Notably, to date, no anaphylactic reactions to bivalirudin have been reported. Moreover, standard ACT assays have been shown to provide satisfactory monitoring of bivalirudin anticoagulation during CPB. In CHOOSE ON-PUMP trial bivalirudin was showed to be a safe and effective anticoagulant in patients with HIT and/or heparin antibodies, whereas in EVOLUTION ON-PUMP trial safety and efficacy was comparable to that of heparin. Taking into account the increased possibility of anaphylaxis after exposure to lepirudin, the unavailability of the ecarin clotting time (ECT) test, and the difficulties the author faced in terms of monitoring anticoagulation and postoperative excessive bleeding, I think that the readers would be interested to know (a) why the bivalirudin was not considered in this particular patient and (b) whether after his described experience the author would consider bivalirudin rather than lepirudin in a similar patient in the future.

MINOR ESSENTIAL REVISIONS

1. Although this is not the main point of interest, the author should briefly discuss the reason for which the patient, given the unusual situation of heparin allergy, underwent OHS for closure of a secundum type ASD rather than percutaneous closure.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Declaration of competing interests:

I declare that I have no competing interests.