Author's response to reviews

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

Authors:

Haralabos Parissis (hparissis@yahoo.co.uk)

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Author's response to reviews: see over
Reviewer 1: D. Angouras

Question 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.

**Answer:**

Dear Reviewer Thank you for your valuable points.

The Paper by Pappalardo et al has been taken into consideration.

Question 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.

Answer:

The introduction has been re arranged as per instructions.

Question 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 rewritings 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 increasing evidence on its safety 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.

**Answer:**

The “discussion” has been amended.
Bivalirudin was not considered in this case because the current evidence regarding the properties of bivalirudin where not known at the time of the reported case.

Furthermore retrospectively, taking into account the increased possibility of anaphylaxis after exposure to lepirudin, the unavailability of the ecarin clotting time (ECT) test in some European institutions (21), and the difficulties we faced in terms of monitoring anticoagulation and postoperative excessive bleeding we would consider bivalirudin rather than lepirudin, in a similar case 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.

Answer:

The reported patient had a large 3 by 4.5 cm secundum ASD requiring patch closure
Reviewer: Friedrich-Christian Riess

This case report is about the use of lepirudin in a patient with suspected heparin allergy undergoing cardiopulmonary bypass for ASD closure.

For anticoagulatory monitoring during cardiopulmonary bypass ACT, aPTT as well as INR was used. Postoperatively, the patient had severe bleeding complications with a need for precipitates and blood transfusion.

It is well known and documented in the literature, that ACT, aPTT as well as INR is not suitable for hirudin monitoring during cardiopulmonary bypass. Ecarin clotting time is the most suitable monitoring test for hirudin dosage during cardiopulmonary bypass. Thus, for me it is not clear, why in an elective ASD closure with suspected heparin allergy. An elective ASD closure was carried out about having ecarin clotting time available in the OI setting.
Moreover, the most cases of heparin so called heparin allergy, the allergic reaction is induced by preservating substances. There are unfractionated heparins available on the market without this substances. Using this special drugs the most cases no allergic reactions would occure.

Thus, I recommend to reject this article because it is an case report on how not to do it.

1. unsufficient preoperative diagnostic (no skin testing of unfractionated heparins free of preservating substances).

2. no ecarin clotting time monitoring system available.

3. Due to unsuitable anticoagulation monitoring system propably overdosage of hirudin with
subsequent severe bleeding complication. It is well documented in many case reports, that lepirudin together with ecarin clotting time monitoring system is a secure technique with a low bleeding risk. I would recommend the author in the future to treat patients only with hirudin having ecarin clotting time available.

Answer:

Dear reviewer, thank you for your comments.

1) The patient developed severe reaction to tinzaparin with bronchospasm and severe anaphylaxis requiring resuscitation.

2) It is well known that the sensitivity of skin testing performed with calcium and sodium Heparin are variable. Furthermore ELISA screening for Heparin/PF4 antibodies is also a not consistent test. In view of the patients previous severe anaphylactic reaction, Increasing IV heparin with pre-emptive administration of methylprednisolone was deemed too risky, due to the previous generalized reaction and the subsequently anticipated dangers involved.

3) the ecarin clotting time needed for monitoring lepirudin concentration is currently not widely commercially available as a point of care test.
However

This is a case report that to the best of our knowledge is the 2nd in the literature that discusses the problem of heparin allergy in a patient requiring CPB. This case is also unique not only because of its rarity but also by the fact that it presents the caveats encountered when ECT is not available. Therefore I do believe that reporting our inadequacies’ allow us to:

Firstly, recognize and diagnose the nature of a particular unfavorable outcome and secondly to learn from it and amend it in our future practice.

Finally the rare nature of the case and its didactic character renders it, in our opinion, worth reporting.

Reference: