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Fondaparinux: another potential treatment for heparin-induced thrombocytopenia type II?

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See related research by Tardy-Poncet et al., http://www.ccforum.com/content/19/1/396

Heparin-induced thrombocytopenia (HIT) type II is a highly morbid and potentially life-threatening condition with limited treatment options in older patients at high risk of bleeding who develop acute kidney injury (AKI). The recent study by Tardy-Poncet et al. [1] showing that argatroban may be a safe and valid therapeutic option in this patient population is therefore of utmost clinical importance. However, when discussing other alternative therapies for HIT type II, the authors did not mention recent experience with fondaparinux, a selective synthetic antithrombin-mediated inhibitor of coagulation factor Xa [2].

Fondaparinux has often been used off-label to treat HIT type II in patients without AKI. Maximal treatment efficacy was obtained in all patients at an approximately six-fold less bleeding risk than in subjects treated with direct thrombin inhibitors (DTIs), including argatroban [3]. As compared with DTIs, fondaparinux therapy is also more user-friendly (intermittent subcutaneous injections instead of continuous infusion) and less expensive. Fondaparinux is predominantly cleared renally. However, accumulation, and hence toxicity, is not expected to occur in patients undergoing renal replacement therapy (RRT). Indeed, because of its low molecular weight (1.7 kDa) and lack of binding to proteins other than antithrombin, fondaparinux should be eliminated easily by all currently used intermittent and continuous RRT techniques in critically ill patients [4]. Moreover, fondaparinux may form a perfect combination with regional citrate anticoagulation to reduce clinical but also dialysis circuit and filter thrombosis [5]. Of course, appropriate guidelines for dose finding, dose modification, and efficacy monitoring of fondaparinux during RRT must be elaborated.

Authors' response

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We read with interest the letter by Honore et al. Even if our study [1] is the first prospective study, there are numerous retrospective studies that reported the efficacy of argatroban in the acute phase of HIT in ICU patients with renal failure and/or hemorrhagic risks. We have not quoted fondaparinux as a therapeutic option because the clinical experience of fondaparinux in HIT patients is still limited despite further previous studies [6–8], especially in ICU patients.

Questions remain regarding the efficacy, safety, and optimal doses of fondaparinux (Table 1). The very long half-life (18 h) of fondaparinux and its accumulation in the case of renal failure both represent major problems in critically ill patients, notably in those with hemorrhagic risk. Indeed, a major bleeding rate of 22 % (six cases among 27) is observed in HIT patients with a high hemorrhagic risk, such as those post cardiac surgery with renal failure (Table 1). Regarding argatroban, continuous infusion cannot be considered a handicap in ICU patients. Moreover, its price can be much reduced when the 250 mg/250 ml argatroban vial is fractionated (under a laminar fluid) in five vials containing 50 mg/50 ml each that will be used over 5 days.

We do agree that fondaparinux could be used as an anticoagulant during hemodialysis. However, there are no convincing data allowing the use of fondaparinux to

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Table 1 Heparin-induced thrombocytopenia patients with/without renal failure and treated with fondaparinux after cardiac surgery

Reference	N	Post cardiac surgery (n)	Renal failure (n)	HIT-associated thrombosis (n)	Major hemorrhage (n)	Duration (days)	Dose (mg/day)
[6]	15	15	14[a]	2	2	8–35	1.5–7.5
[7]	11	11	10[b]	3	3	4–17	2.5–7.5
[8]	16	11	3[c]	9	1	2–35	2.5–15

HIT Heparin-induced thrombocytopenia
[a]Eleven patients with creatinine clearance <30 ml/min
[b]Eight patients with creatinine clearance <30 ml/min
[c]One patient with creatinine clearance <30 ml/min

prevent or treat clinical thrombosis in the acute phase of HIT, especially in ICU patients.

Abbreviations
AKI: Acute kidney injury; DTI: Direct thrombin inhibitor; HIT: Heparin-induced thrombocytopenia; RRT: Renal replacement therapy.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
PMH and HDS designed the article. PMH, RJ, IH, EDW,VVG, and HDS participated in drafting the manuscript. All authors read and approved the final version.

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