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Adequate Management of Heparin-Associated Thrombocytopenia

Dear Sir,

In a recent issue of *Nephron* Berlot and Lucchese [1] reported their management of heparin-associated thrombocytopenia (HAT) during continuous venovenous hemofiltration. They described a case of rapid onset of severe thrombocytopenia after initiating intravenous heparin therapy and stated 'that the diagnostic criteria for HAT have been completely fulfilled'. Despite of that, they reported a continuation of heparin therapy at lower doses without recovery of platelet counts at that stage and at last the slow return of platelet counts into the normal range more than 1 week after finishing intravenous heparin therapy. With reference to the current literature and the clinical experience in our hospital, this approach does not seem to be adequate.

Up to 10% of the patients receiving heparin therapy develop a decrease in platelet counts [2–4]. According to Chong [5], two types of this common adverse effect have to be distinguished:

HAT type I usually is harmless and occurs shortly after initiation of heparin therapy. Thrombocytopenia usually is mild, platelet counts rarely drop to values below 100,000/ μ l or less than 30% of initial values. Though its precise nature is not clear at present, it does not seem to be of immunologic origin and has been ascribed to an intrinsic proaggregatory effect of heparin. HAT type I usually will resolve without cessation of heparin therapy. Clinical complications are rare.

By contrast, HAT type II is a potentially lethal complication of heparin therapy. Prospective studies approximate the incidence of this disease to 1–2% among patients re-

ceiving high-dose ($>20,000$ IU/24 h) unfractionated porcine heparin therapy for more than 5 days [3]. Platelet counts may decrease down to 50,000/ μ l or less or may drop to less than 50% of initial values. The fall of platelet counts usually occurs 5 or more days after initiation of heparin therapy. But if heparin therapy has been already performed in the patient's past (a fact that can only seldomly be excluded with appropriate certainty), HAT II may occur much earlier. Without adequate management HAT II causes arterial as well as venous thromboses. According to one review including 85 patients, these led to an amputation of a limb in 20% of the cases; 30% (!) of the patients died [2]. In contrast to HAT I, HAT II is an immunological complication of heparin therapy. In the majority of the cases antibodies are raised against complexes of heparin and platelet factor 4 (PF4) [6–8]. In some HAT II patients antibodies against the PF4-related chemokines interleukin 8 or neutrophil-activating peptide 2 cause the disease [9]. For details on pathophysiology the reader is referred to the literature.

Once the diagnosis is suspected, immediate stop of heparin therapy is mandatory [4]. A switch from unfractionated heparin to low molecular weight heparin is not sufficient, as several studies have shown a high cross-reactivity rate of low molecular weight heparin with the anti-heparin/PF4 antibody in HAT II patients [10, 11].

In addition to prostacyclin, a number of alternative therapeutic approaches have been evaluated in the past [12–16]. None of these has been established in clinical practice so far. Instead, since its first description in

1983 [17], the low molecular weight heparinoid danaparoid (Org 10172, Orgaran®) up to now is the most widely used agent [18, 19]. Its anticoagulative effect is mainly based on the inhibition of activated factor X. In our population of critically ill patients demanding continuous venovenous dialysis procedures as well as in the population on maintenance hemodialysis, this therapeutic alternative is safe and can be monitored by the measurement of anti-factor Xa activity. The usage of danaparoid is compromised by two disadvantages: (1) there exists a cross-reactivity of the HAT II antibodies towards this agent in approximately 10% of the cases, and (2) its anticoagulative half-life is quite prolonged, especially in end-stage renal disease. As therapeutic alternative recombinant hirudin (lepirudin; HBW 023, Refludan®) has proven its clinical usefulness as parenteral safe anticoagulant in different prospective studies [20–22]. Lepirudin is now approved in the European Community for the treatment of HAT type II. Recombinant hirudin is the most potent direct selective thrombin inhibitor known so far. Its anticoagulative activity can easily be monitored with the activated partial thromboplastin time. Elimination of recombinant hirudin essentially depends on renal function. In patients with renal impairment its dose, therefore, has to be carefully titrated. Like in the case of danaparoid, its elimination half-life is significantly prolonged in end-stage renal disease. As recombinant hirudin and heparin are structurally not related, a cross-reactivity of HAT II antibodies towards recombinant hirudin does not exist.

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It is often impossible to distinguish HAT type II from other forms of thrombocytopenia using clinical criteria alone: therefore, these are not sufficient for the diagnosis of HAT type II. Instead, early testing for HAT II antibodies is imperative [4]. Specific tests are available in sophisticated centers [23].

In summary, adequate management of HAT type II should include: (1) Immediate termination of heparin therapy when diagnosis is suspected; (2) switch to one of the aforementioned therapeutic alternatives, if parenteral anticoagulation still is needed; (3) in parallel test for HAT II antibodies; (4) in case diagnosis of HAT II is verified, clear documentation to exclude reexposure of the respective patient to heparin, and (5) if further necessary, early initiation of an oral anticoagulation. However, until the therapeutic range is reached, a compatible, parenteral anticoagulation should be continued.

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