Taking advantage of the non-anticoagulant effects of heparin
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In this issue of Thrombosis and Haemostasis Joglekar et al. (1) assessed a partially desulfated heparin (ODSH) and its interaction with platelet factor 4 (PF4) in regard to the pathogenesis of heparin-induced thrombocytopenia (HIT). Joglekar et al. show by a series of elegant experiments that ODSH and unfractionated heparin (UFH) are similar with respect to PF4 binding but different in respect to exposure of the HIT-antigen. These charge-dependent interactions of ODSH and PF4 may have important therapeutic implications in HIT.

ODSH was not designed to be a heparin substitute, at least not for its conventional use as an anticoagulant. ODSH is obtained by desulfation of unfractionated heparin at positions 2-O and 3-O of D-glucosamine-N-sulfate. 3-O sulfation is essential for the interaction of heparin with antithrombin and its desulfation reduces binding affinity of heparin to antithrombin \( \sim 20,000 \times \) (2). While ODSH has only minimally anticoagulant activities, the remaining negative charges of ODSH allow it to interact with a number of positively charged proteins that are critical for mediating other anti-inflammatory effects of heparin. In the case of HIT, these interactions between ODSH and positively charged proteins can be exploited to interfere with complex formation between heparin and PF4, the main antigen in HIT. Using in vitro and in vivo approaches, Joglekar et al. show that when ODSH is incubated with UFH, ODSH disrupts PF4/H complex formation and interferes with both, HIT antibody binding and immunogenicity of PF4/H complexes in a mouse model. These studies complement recent findings by Krauel et al. (3), who also showed inhibition of PF4/heparin complex formation and HIT antibody binding by ODSH. Both studies imply that ODSH might be used as an additive to heparin to reduce immunogenicity of heparin and could potentially be used for treatment of acute HIT. A very intriguing clinical setting for the use of ODSH in acute HIT would be patients, who develop HIT after insertion of a heparin-coated vascular graft. In these patients, currently, explantation of the heparin-coated graft becomes sometimes necessary (4–6). As PF4/heparin antibodies usually decline within weeks despite continuation of heparin (7), co-administration of ODSH until the antibodies have disappeared may prevent graft removal and potential limb loss.

In a pivotal study, Petitou et al. (8) have shown that by drug design and specific positioning of sulphate groups, the anticoagulant properties of heparin can be maintained, while omitting several other biological effects of heparin. The concept of ODSH is the opposite. ODSH preserves the non-anticoagulant properties of heparin while minimizing the anticoagulant properties of heparin and lowering the risk of bleeding. The non-anticoagulant properties of ODSH may also be useful for maximising therapeutic effect of other anticoagulant agents, such as fondaparinux. Fondaparinux is highly specific for antithrombin and seems to be a promising alternative drug for treatment of patients with acute HIT (9). However, fondaparinux was associated with an increased risk of guide catheter thrombosis in patients undergoing coronary interventions and was shown to be ineffective in preventing clotting activation initiated by the contact activation pathway (factors XII and Xa) on coronary artery catheters (10). Potentially, addition of ODSH to fondaparinux (or other non-heparin anticoagulants) can safely substitute some of the non-anticoagulant effects of heparin. One of the most attractive clinical scenarios to test this would be addition of ODSH during citrate dialysis (12).

References


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