Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Citation for published version (APA):
de Pont, A-CJM. (2006). Anticoagulation in severe sepsis and the multiple organ dysfunction syndrome

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Download date: 14 Dec 2018
Chapter 10

Summary
Sepsis and the multiple organ dysfunction syndrome represent important problems in intensive care medicine because of their high incidence and mortality rate. In the Netherlands, sepsis and multiple organ failure carry an annual intensive care unit admission rate of approximately 8500, with a mortality rate of 38%. In the pathogenesis of both sepsis and the multiple organ dysfunction syndrome, coagulation plays an important role.

In this thesis, the results of a number of studies concerning the effect of anticoagulation in severe sepsis and the multiple organ dysfunction syndrome are reported, using both a human endotoxemia model and clinical settings.

In **Chapter 1**, the current knowledge about the role of anticoagulation in the treatment of severe sepsis and the multiple organ dysfunction syndrome is reviewed. The first part of the thesis, consisting of the chapters 2 - 4, focuses on the extrinsic coagulation pathway and the role of activated protein C during human endotoxemia and sepsis. The second part of the thesis, consisting of the chapters 5 - 9, assesses the effects of anticoagulation during continuous renal replacement therapy, which represents the main indication for anticoagulation in patients with the multiple organ dysfunction syndrome.

In **Chapter 2**, we describe the effects of recombinant Nematode Anticoagulant Protein c2 (rNAPc2), a potent inhibitor of the tissue factor/factor VIIIa complex, on parameters of coagulation and inflammation in a human endotoxemia model. The administration of rNAPc2 completely blocked endotoxin-induced thrombin generation, as measured by plasma prothrombin fragment F1+2, without an effect on fibrinolysis. In addition, the administration of rNAPc2 attenuated the endotoxin-induced increase in interleukin-10, without affecting the increase in other cytokines.

In **Chapter 3**, we report the finding that endotoxin is able to elicit a transient resistance to activated protein C (APC), which lasts approximately 24 h and is predominantly mediated by an increase in factor VIII. This finding suggests that APC-resistance might play a role in the procoagulant state occurring during human endotoxemia.

In **Chapter 4**, the effects of treatment with recombinant human activated protein C (rhAPC) on parameters of coagulation and inflammation in severely septic patients are described by comparing rhAPC-treated patients to case controls. Sepsis-induced thrombin generation was reset by rhAPC within the first 8 h of treatment, without an effect on parameters of fibrinolysis and inflammation. This finding might have important consequences for the recommended duration of rhAPC treatment in patients with severe sepsis.
The effects of predilutional continuous venovenous hemofiltration (CVVH) without anticoagulants on parameters of coagulation are reported in Chapter 5. We found an increase in thrombin generation during CVVH in a subset of patients with significantly lower baseline parameters of contact activation. As fibrinolysis is at least partially contact activation dependent, it is conceivable that in the subset of patients with a relatively impaired contact activation, the attenuation of fibrinolysis leads to enhanced thrombin generation during CVVH. In circuits running shorter than the median of 7.4 h, the increase in thrombin generation was inversely correlated with circuit survival time.

In Chapter 6, predilutional and postdilutional CVVH are compared with respect to extracorporeal circuit thrombogenesis and clearance. In this study, predilution and postdilution were similar with respect to extracorporeal circuit thrombogenesis. No signs of platelet activation or increased thrombin generation were found during either mode. Urea clearance was 30% higher during postdilution, at the expense of higher extracorporeal circuit pressures. We demonstrated that during postdilution, a linear relationship existed between baseline platelet count and maximal prefiltre pressure and that both parameters inversely correlated with circuit survival time. This suggests that baseline platelet count has an important impact on maximal prefiltre pressure and thus on circuit survival time during postdilution.

We compared similar doses of two low molecular weight heparins, nadroparin and dalteparin, during high-volume postdilutional CVVH and reported the results in Chapter 7. This study demonstrated that nadroparin and dalteparin are bioequivalent with respect to their anti-Xa activities. No relationship was found between circuit survival time and anti-Xa peak activity or area under the plasma concentration versus time curve for 0-3 h. However, there was a strong trend towards an inverse correlation between baseline platelet count and circuit survival time.

In Chapter 8, our experience with CVVH during rhAPC treatment is described by comparing rhAPC to unfractionated heparin as the sole anticoagulant during CVVH, each patient being its own control. Circuit survival times were similar during anticoagulation with either rhAPC or unfractionated heparin.

Finally, in the last chapter a guideline for anticoagulation with unfractionated heparin and low molecular weight heparins during CVVH is formulated, based on a review of the literature. Pros and cons of both unfractionated heparin and low molecular weight heparins are discussed.