Karolinska Institutet

Department of Clinical Science, Intervention and Technology (CLINTEC), Division of Pediatrics

Coagulation in children with liver disease

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssal R64, plan 6, Karolinska Universitetssjukhuset Huddinge

Fredagen den 15 februari 2013 kl. 10.00

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Stockholm 2013

ABSTRACT

About 100 new children in Sweden require care at a tertiary pediatric ward each year for severe liver disease. These children are at risk for both severe gastrointestinal bleeding, which may be life threatening, and intra- or extrahepatic thrombosis. Both pro- and anticoagulant factors are synthesized in the liver and their levels decrease as liver failure progresses. Coagulation factors are thus used as prognostic tests. The balance between pro- and anticoagulant mechanisms, although maintained in liver disease, seems to be instable and can easily tip towards either bleeding or thrombosis. The coagulation system in children undergoes age-specific changes and the etiology and/or pathogenesis of pediatric liver diseases is different than in adults.

The aims of this thesis were to improve the treatment and the analysis of coagulation defects in pediatric liver disease and also to improve the prognostic evaluation in liver disease.

In **Study 1** children with liver disease were treated with recombinant FVIIa due to life threatening bleeding or as prophylaxis prior to invasive procedures. In the first group, the bleeding decreased in 50% of the evaluated occasions and a combination of rFVIIa and octreotide in gastrointestinal hemorrhage was advantageous. In the second group, rFVIIa was useful as prophylactic treatment before various diagnostic and therapeutic procedures.

In **Study 2** the thrombin generation test was evaluated in children with liver disease, with and without increased bleeding risk. The results were compared to age-matched healthy controls. This assay did not provide additional information compared to routine coagulation tests.

In **Study 3** the correlation between bile acids and coagulation factors was investigated. In children with markedly elevated levels of bile acids, i.e. above 200 µmol/L, the levels of coagulation factors increased with rising levels of bile acids, despite a worse clinical outcome. In an in vitro study, no interference between bile acids and coagulation factor concentrations was detected.

In **Study 4** the Owren method for analyzing INR in patients with liver disease was assessed. Plasma samples from adult patients with liver disease were analyzed at eight laboratories. The coefficient of variance between the laboratories was 5.3%, which is low. Additionally, the ISI_{VKA} and ISI_{liver} were determined and the difference between them was below 10%. These results show that the previously reported high interlaboratory variability regarding INR in patients with liver disease does not constitute a problem when Owren-based reagents are used.

Conclusion: rFVIIa is beneficial for selected patients with severe bleeding and as prophylactic treatment. However, with current knowledge regarding coagulation in liver disease, new treatment strategies aiming to maintain the hemostatic balance in critical situations need to be studied. The thrombin generation test did not provide more information than routine tests. A modified method might be more successful. Coagulation factors may be questionable as prognostic markers in patients with highly elevated bile acids. The mechanisms behind the effect of high bile acids on the coagulation system are very important targets of further studies. Finally, Owren-based reagents for measurement of INR in patients with liver disease provide a solution to the problem with high interlaboratory variability seen internationally.

This thesis adds important information regarding several aspects of the coagulation in children with liver disease and highlights directions for future research.

Keywords: FVIIa, thrombin generation, cholestasis, bile acids, prognosis, INR, ISI, Owren