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PROPHYLAXIS OF THROMBOEMBOLISM DURING PREGNANCY IN THREE SISTERS WITH CONGENITAL ANTITHROMBIN III (AT III) DEFICIENCY COMBINED WITH REDUCED INDUCIBLE FIBRINOLYTIC ACTIVITY. U. Schoch, E. Zanetti, A. von Felten. Laboratory of Blood Coagulation, Dept. of Internal Medicine, University Hospital, Zürich, Switzerland.

AT III deficiency is associated with a high risk of venous thromboembolism, particularly in pregnancy. As prophylactic treatment it has been recommended to normalize plasma levels of AT III by use of AT III concentrates, besides giving heparin.
We report on the prophylactic treatment of three sisters (age 21, 25, 32 years) with congenital AT III deficiency (38-53%, normal: 80-120%) as well as a reduced inducible fibrinolytic activity (1.2, 5.8, 7.9%, normal: >8.5%), who already had suffered from severe thromboembolism. During pregnancy prophylactic measures were taken individually, depending on the plasma level of β-thromboglobulin (BTG) determined every 2-3 weeks. At the time of the first increase of BTG (around 10th week of gestation) prophylaxis with s.c. heparin 2x7'500IU/d was started, leading to normalization of BTG. When BTG was again elevated, the dose of heparin was successively increased up to 2x15'000IU/d; thereby, functional AT III levels remained in the range of 28-50%. Two patients received only heparin throughout the pregnancy. However, in one patient BTG levels could not be normalized by heparin alone (60-130ng/ml, normal: <43ng/ml). Injections of AT III concentrate, 1'000IU, led to reduction of BTG within 2 hrs (60 → 42, 220 → 61 ng/ml). Therefore, AT III was given from the 25th week of gestation in increasing amounts up to 5'000IU/week (funct. AT III in plasma: 51 - 72%) in addition to heparin (2x12'500IU/d), resulting in BTG levels of 33-51 ng/ml. From the onset of labour, all patients received AT III concentrates (two patients 1'000IU every second day, one patient 1'000IU daily) together with i.v. heparin 20'000-27'500IU/d, until the oral anticoagulant treatment started after delivery had reached therapeutic levels. The amount of AT III concentrate totally administered was 5'000IU in two patients and 66'000IU in one patient. None of the patients showed ever signs of venous thrombosis.
Our observations demonstrate that instead of an AT III substitution with the aim to normalize its plasma level, an effective thrombosis prophylaxis - monitored by plasma levels of BTG - may be achieved with heparin alone or combined with low amounts of AT III concentrate.

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RANDOMIZED TRIAL OF ANTITHROMBIN III VERSUS PLACEBO IN PATIENTS UNDERGOING PERITONEO-VENOUS SHUNT OPERATION. C. Korninger (1), W. Klepetko (2), J. Miholic (2), Ch. Schwarz (2) and K. Lechner (1). 1st Dpt. of Medicine (1) and 2nd Dpt. of Surgery (2), University of Vienna, Austria.

A randomized trial of Antithrombin III (AT III) versus placebo was performed in patients undergoing peritoneo-venous shunt operation because of intractable ascites. 10 patients with alcoholic liver cirrhosis (Child's stages B and C) were enrolled. Randomization was performed according to the stage of liver disease and to preoperative AT III levels. AT III concentrate (kindly provided by Kabi) was infused in 5 patients, twice daily for 4 days, at a dose of 20 U/kg BW, starting 12 hours prior to operation. Coagulation studies were performed preoperatively, and on postoperative days 1, 3 and 7.

		preop.	day 1	day 3	day 7
No AT III	AT III (%)	60±26	43±18	46±13	58±26
Substitution	Fgn (g/l)	4.1±1.9	2.5±1.3	2.4±1.1	2.6±1.5
(n=5)	Plts (10^9/l)	128±85	84±59	71±55	103±82
AT III	AT III (%)	58±18	63±13	83±15	63±25
Substitution	Fgn (g/l)	4.0±1.2	3.2±1.2	3.5±2.4	3.0±1.8
(n=5)	Plts (10^9/l)	164±108	99±54	106±69	121±100

In all patients, ethanol gelation test was positive on postoperative days 1 and 3, indicating the presence of fibrin monomers. No difference between the two groups was seen with respect to prothrombin times, coagulation factor levels, FPA concentrations or fibrinolysis parameters. It is concluded that the severity of disseminated intravascular coagulation can be tempered by AT III substitution, but, with the administered dosage, DIC cannot be prevented.

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COMPARATIVE STUDIES ON ANTITHROMBIN III AFFINITY OF LOW MOLECULAR WEIGHT HEPARIN AND UNFRACTIONATED HEPARIN. N Sakuragawa, T. Shimotori and K. Takahashi. Central Clinical Laboratory, Toyama Medical and Pharmaceutical University, Toyama, Japan.

Purpose: Low molecular weight(LMW)heparin shows stronger anti-factor Xa(F-Xa) and weaker anti-thrombin(TH) activities compared with unfractionated(UF) heparin, and shows less bleeding tendency in the cases of clinical use. These characteristics were surmised to be depend on antithrombin III(AT-III) affinity of the heparin.
Materials and methods: LMW heparin(Kabi and Pharmuka), UF heparin (Novo) and heparin cofactor II(HC-II) purified by our method were used. AT-III affinity column chromatography with 0.1 M Tris-buffer (pH 7.4)-NaCl 0.02 to 2.5 M linear gradient was performed. From the point of AT-III affinity strength, non-affinity(Na), low affinity(La) and high affinity(Ha) were separated, and aPTT, anti-F-Xa and anti-TH activities were assayed on each fractions. HC-II was assayed by biological activity.
Results: (1) Kabi-LMW heparin; Na 34.5%, La 39.3%, Ha 26.2%, Pharmuka-LMW heparin; Na 58.0%, La 24.1%, Ha 17.3%. Novo; Na 0%, La 50%, Ha 50%. (2) APTT; Na showed no effect, but Ha showed the strongest prolonging effects on aPTTs even having less amount of uronic acid, and more prominent effects were observed in UF(Novo)-heparin than LMW heparins. (3) La showed higher activity of anti-F-Xa and anti-TH activities than Ha. (4) Anti-TH activity of AT-III was observed in both fractions of La and Ha, but that of HC-II was observed in each fractions including Na.
Conclusion: It was surmised that the differences of the characteristics between LMW heparin and UF heparin were depend on to the strength of AT-III. The different characteristics of HC-II from AT-III to anti-TH were observed and surmised to be depend on the binding ability to the fractions.

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INTERACTION BETWEEN CULTURED ENDOTHELIAL CELLS AND ABNORMAL ANTITHROMBIN III "TOYAMA". N.Sakuragawa, S.Saitoh and K.Takahashi. Central Clinical Laboratory, Toyama Medical and Pharmaceutical University, Toyama, Japan.

Purpose: Abnormal antithrombin III(AT-III)Toyama showed non-affinity to heparin and heparinoid to show loss of immediate antithrombin activity. On the endothelial cells, there are heparinoids including heparan sulfate. We investigated on the interaction between cultured endothelial cells and abnormal AT-III"Toyama" from the viewpoint of antithrombin activity.
Materials and methods: (1) Endothelial cell culture: ^{125}I-labelled normal and abnormal AT-III were placed on the washed endothelial cultured cells in 0.2 ml of RPMI-1640 medium for 15 min at 37°C. The medium was suctioned off and the cell layer was washed with Hank's balanced salt solution. The cells were incubated with 1 ml of heparin(3 ug/ml) for 15 min at 4°C. The radioactivity in the supernatant was counted, and represented AT-III which bound to the cells surface. (2) Antithrombin activity: 0.23 ml of thrombin solution(5 U/ml) and 0.03 ml of normal or abnormal AT-III plasma were mixed, and incubated on the cultured cell surface for 5 min at room temperature. The residual thrombin activity was assayed by 0.3 ml of the substrate (S-2238) solution(0.8mM)for 5 min. After these procedures,2 ml of 2% citric acid solution was added to stop the reaction, and OD(405 nm) was recorded.
Results: Abnormal AT-III showed reduced binding-activity to cultured cells to one fifth compared with normal AT-III, and the residual thrombin activity in the abnormal was higher compared with that in normal plasma.
Conclusion: Abnormal AT-III showed less binding activity to the cultured endothelial cells, and less thrombin neutralizing activity to show thrombogenic tendency.