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CLINICAL RELEVANCE OF D.DIMER AND COAGULATION INHIBITORS IN LIVER CIRRHOSIS.

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D.Dimer was measured by a latex agglutination assay and an enzyme immunoassay (E.I.A.) in 25 patients suffering from liver cirrhosis. High levels of D.Dimer (> 500 ng/ml) were found in 13/25 patients' plasma, by the latex test as well as EIA. Fibrinogen Degradation Products (FDP), measured by the Merskey method, were present in 7/25 samples, whereas soluble fibrin monomer complexes were only detected in 2/25 patients. In both cases, D.Dimer was elevated and FDP were in the normal range. Only one patient developped a Disseminated Intravascular Coagulation (DIC). None of the others had any thromboembolic event.

Anticoagulant plasma proteins, Protein C (pC), total and free Protein S (pS) and Antithrombin III (AT III), were measured, in these patients, using the Laurell method.

Mean values measured were :

AT III : 50 % ± 16 total pS : 69 % ± 20
pC : 38 % ± 28 free pS : 63 % ± 30

Using immunoassays, pS showed the lowest decrease, in comparison to the other coagulation inhibitors.

These values were compared to some procoagulant activities : prothrombin, factors VII + X and factor V.

A good correlation was observed between AT III and prothrombin ($r = 0.752$ $p < 0.01$), whereas a poorer one was obtained between pC and factors VII and X ($r = 0.455$ $p < 0.02$). There was no correlation between pC and pS, nor between pC and factor V.

Despite marked decrease of coagulation inhibitors in liver cirrhosis, low incidence of thrombotic accidents was observed (1/25) probably due to a parallel decreased synthesis of procoagulant factors. However, an in vivo blood activation associated to a reactive fibrinolysis was evidenced by measurement of pathological levels of D.Dimer in 13/25 patients. In this way, D.Dimer is a more sensitive and specific marker, than total FDP, to evaluate blood activation in liver cirrhosis. D.Di Test allows a rapid estimation and gives similar results to the EIA method.

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LEVELS OF D-DIMER FRAGMENT OF FDP IN CASES OF ACUTE PROMYELOCYTIC LEUKEMIA WITH NORMAL LEVELS OF ANTITHROMBIN III AND PROTEIN C IN PLASMA.

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16 cases of acute promyelocytic leukemia (APL), with prolongation of prothrombin time, depletion of fibrinogen in plasma and marked increase in fibrin/fibrinogen degradation products (FDP) in serum, were compared with 8 cases of disseminated intravascular coagulation (DIC) caused by other diseases than APL. In the cases of APL, levels of plasminogen and α_2-antiplasmin in plasma strikingly decreased and concentrations of α_2-antiplasmin-plasmin complex in plasma markedly increased. However, levels of antithrombin III and protein C in plasma of these cases were within normal limits or only slightly decreased. In these cases, hepatic or renal dysfunction was not observed. Further investigation revealed that a marked depletion in factor XIII activity and a striking increase in levels of D-dimer fragment of FDP (including YD fragment etc.) were present in the cases of APL. Significant correlations between levels of D-dimer and FDP measured by the conventional method were also observed. From these results, it is concluded that DIC is present in the cases of APL, although relevance to fibrinolysis is strongly suggested. However, it remains obscure concerning to etiology of normal or only slightly reduced levels of antithrombin III and protein C in the cases of APL.

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D-DIMERS: A MONITORING PARAMETER IN THROMBOLYSIS?

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D-dimers are specific derivatives of cross-linked fibrin. Their concentration may be used to conduct thrombolysis and predict its outcome. In this investigation we studied the relationship between D-dimer plasma levels during thrombolysis of deep leg vein thrombosis (DVT) and the phlebographic success.

METHODS: 17 patients (9 males, 8 females, age range 17-56 years) were studied. All patients had DVT and were treated with either an acylated streptokinase-plasminogen complex (n=10) or streptokinase (n=5) or both drugs successively (n=2) for 4.6 days on average. The thrombolytic effect was assessed by ascending phlebography and the patients were divided into 3 groups: A complete clearance, B partial clearance, C no change. The D-dimers were measured by a non-competitive EIA assay with a monoclonal antibody against a conformational epitope on the plasmin-resistant D-dimer fragment of cross-linked fibrin.

RESULTS: The table gives the mean D-dimer levels in the 3 groups of patients at 12 hours intervals.

Hours	0	12	24	36	48	60	72	84	96	108	120	132
A(n=7)	1.9*	5.6	9.2	6.5	5.6	5.7	4.0	3.6	4.2	4.1	4.0	2.8
B(n=6)	3.7	5.7	5.8	4.4	3.8	3.5	4.6	3.9	3.6	2.9	1.5	1.3
C(n=4)	1.0	2.9	2.9	3.6	5.0	4.9	5.4	5.0	2.6	1.8	1.3	1.1

*units µg/ml (normal range: under 0.2µg/ml)

The statistical analysis (Newman-Keuls multiple range test) suggests that low D-dimer levels, especially over the first 36 hours are related to treatment failures.

CONCLUSIONS: Despite some overlapping between successful and non-successful cases and lack of absolute specificity of the assay the D-dimer concentration may predict treatment failure in the first two days.

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FIBRINOLYTIC RESPONSE TO VENOUS OCCLUSION, AND FIBRIN FRAGMENT D-DIMER AND FIBRONECTIN LEVELS IN NORMAL AND COMPLICATED PREGNANCY.

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The fibrinolytic response to venous occlusion was assessed in pregnant women with measurements of total and free t-PA, using specific ELISAs based on monoclonal antibodies.

Total t-PA levels increased after venous occlusion with 11 ± 8 ng/ml (mean ± SD) in healthy fertile non-pregnant women (n=6), with 0.8 ± 1.3 ng/ml in 2nd trim. (n=5) and with 3.8 ± 3.9 ng/ml in 3rd trim. (n=4) healthy pregnant women. The increase in free t-PA was 12 ± 11; 1.2 ± 0.9 and 0 ng/ml respectively. The difference in post- and pre-occlusion levels in 3rd trim. pregnant women with insulin dependent diabetes mellitus IDDM (n=4) was 3.2 ± 4.2 ng/ml, with intrauterine growth retardation (IUGR) (n=4) 2.6 ± 3.0 ng/ml and with preeclampsia (n=5) 3.2 ± 3.5 ng/ml for total t-PA and 0, 0 and 0 ng/ml for free t-PA.

Fibrin fragment D-dimer levels in plasma measured with a specific ELISA were 130 ± 36 ng/ml in healthy fertile non-pregnant women (n=8). A significant increase was found in 4 out of 5 1st trim., 25 out of 25 2nd trim. and 21 out of 22 3rd trim. normal pregnant women. In these groups, plasma levels were 340 ± 160, 400 ± 170 and 440 ± 220 ng/ml respectively.

Fibronectin levels, measured with a Laurell electroimmunoassay and expressed as percentage of pooled human plasma (=330 µg/ml) were 83 ± 26% in 2nd trim. patients (n=24) and 102 ± 35% in 3rd trim. patients (n=17). Normal fibronectin levels were found in 4 patients with IDDM and in 6 with IUGR, whereas in 6 out of 8 preeclamptic patients significantly increased levels were observed.

These results confirm, with the use of a newly developed free t-PA assay, that the fibrinolytic response to venous occlusion is completely inhibited in the 3rd trimester of pregnancy. A reduced release of t-PA from the vessel wall during venous occlusion and/or an increased inhibition of released t-PA were observed. No difference was found in the fibrinolytic response between normal and complicated pregnancy. D-dimer levels are significantly elevated during pregnancy. Finally, the usefulness of fibronectin for the diagnosis of preeclampsia is confirmed.