Influence of Fluvastatin on Levels of von Willebrand Factor in Cardiac Transplant Recipients

Dear Sir,

Ambrosi et al (1) recently reported levels of various endothelial markers in cardiac transplant recipients before and after being placed on the lipid-lowering agent fluvastatin. This intervention reduced levels of cholesterol and soluble thrombomodulin (both p <0.001) but, despite this, there was no difference in levels of von Willebrand factor. Our colleagues found this failure to respond puzzling, and suggest that von Willebrand factor may be a marker of endothelial activation or inflammation than of injury.

All the subjects in the study were taking the immunosuppressive drug cyclosporine, and 60% were taking the cytotoxic drug azathioprine. It has been shown that the cyclosporin vehicle, cremophor, enhances stimulated release of von Willebrand factor by human umbilical cord endothelial cells in vitro (2). Consequently, if the same effect is present in vivo, this can simply explain the failure of von Willebrand factor to respond to the reducing levels of cholesterol. Licciardello et al (3) showed that von Willebrand factor increased when patients with squamous-cell carcinoma were placed on cisplatin-based chemotherapy. If the same phenomenon is true for azathioprine than this is a further reason for finding increased von Willebrand factor that does not respond to lipid-lowering therapy.

It follows that if the endothelium is being damaged by cyclosporin, azathioprine and other agents, then changes in levels of soluble thrombomodulin must be responding to a different stimulus and are unresponsive to chemotherapy. This latter possibility is partially supported by our data from subjects undergoing bone marrow transplantation (4). Although both von Willebrand factor and soluble thrombomodulin were raised compared to controls in the 25 patients before transplantation, levels of von Willebrand factor increased further after transplantation (a likely response to the total body irradiation, cyclophosphamide and other agents including some cyclosporine) but there was no change in levels of soluble thrombomodulin.

Thus our study, and that of Ambrosi et al, underline the importance of considering the possible deleterious effects of drugs on the endothelium, and that the factors involved in the release of von Willebrand factor are distinct from those controlling soluble thrombomodulin. As former is not a membrane constituent, being stored in intra-cellular organelles, and the latter is a membrane glycoprotein, these differences are entirely understandable.

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Received April 10, 2000 Accepted April 17, 2000

Prevalence of Clotting Factor Deficiencies in a Large Population with von Willebrand Disease

Dear Sir,

We read with interest the letter by Bux-Gewehr and colleagues (1). The authors reported a prevalence of 10% of FXII deficiency in a population of 270 patients with von Willebrand disease (VWD) compared to 1.5% found in healthy blood donors. We found these findings surprising and not in agreement with our experience which is reported here.

At the Royal Free Hospital Haemophilia Centre a total of 435 patients are registered with VWD and regularly followed-up (2). A retrospective analysis showed that only 125/435 (28%) patients had a prolonged APTT (> 38 sec). Among this subgroup seven (5%) patients were found to have associated clotting factors deficiencies: two had a partial FXII deficiency (35 IU/dl and 42 IU/dl, respectively, NR: 50-150 IU/dl) and five had partial FXI deficiency (median FXI 60 IU/dl, range 44-68

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Received April 10, 2000 Accepted April 17, 2000
IU/dl, NR:70-150 IU/dl). In a further four patients the prolonged APTT was accounted for by the presence of inhibitors: lupus antibodies (two patients), acquired VWF inhibitors (one patient) and allo antibodies to VWF (one patient). In the remaining patients there was no evidence of other associated clotting factors deficiencies and the prolonged APTT was probably due to decreased FVIII levels in the context of VWD.

In patients with VWD and a family history of other clotting factor deficiencies the respective factors were investigated despite a normal APTT. In those we found that 10 additional patients had an associated partial FXI deficiency (median FXI 61 IU/dl, range 41-70 IU/dl) and two patients had an associated mild FIX deficiency (29 IU/dl and 35 IU/dl, respectively; NR: 50-150 IU/dl). Thus, in total, 19/435 (4%) patients with VWD were found to have an associated clotting factor deficiency. Of note, all patients with combined deficiencies had type I VWD.

According to our findings, FXII deficiency is rare among patients with VWD (0.4%). Therefore, we do not agree with Bux-Gewehr and colleagues who suggested that FXII level should be determined in every diagnostic work-up of patients with VWD with a prolonged APTT, particularly when the APTT is used to monitor therapy. Moreover, using the APTT to monitor therapy is probably suboptimal and the determination of FVIII and/or VWF activity levels is usually required. In addition to its low prevalence, the association of FXII deficiency does not apparently influence the course of VWD (1).

Other clotting factors deficiencies involved in the intrinsic coagulation pathway were found with a similar (FIX) or higher (FXI) frequency than factor XII deficiency. Regarding factor XI, the high prevalence in our cohort also reflects the ethnic background of our catchment area with a large Ashkenazi Jewish community. In contrast to factor XII, associated FIX and FXI deficiencies did influence the type and severity of the bleeding pattern and more importantly the management of the affected individuals.

In conclusion, when finding a prolonged APTT in a patient with VWD, investigation for factor XII deficiency should not be a priority, as it is rare and without clinical significance, in contrast to other combined deficiencies with FIX or FXI.

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Received April 10, 2000 Accepted April 17, 2000

Thromb Haemost 2000; 84: 515-7

Human Herpesvirus 8 Infection in Haemophiliacs

The newly identified human herpesvirus 8 (HHV-8) is the likely etiologic agent of Kaposi’s sarcoma (KS) and is associated with the body cavity-based lymphoma (BCBL), a rare subtype of non-Hodgkin’s lymphoma) and the multicentric Castleman’s disease (proliferation of lymphoid tissue) (1, 2). Sexual transmission seems to be the main route for viral spread, but organ transplantation and blood transfusion may be also at risk of transmitting HHV-8 infection (3). Recent reports have demonstrated the presence of viral genome in peripheral blood mononuclear cells from European and African blood donors (4, 5), as well as the presence of potentially infectious virus in CD19+ (B) cells from a North American blood donor (6). Most surprisingly, two studies have reported a lower HHV-8 seroprevalence in haemophiliacs than in blood donors. For US haemophiliacs, an HHV-8 seroprevalence rate of 12% (10/83) was determined, and a rate of 20% (9/44) in blood donors (7). In a cohort of British haemophiliacs, seropositivity was 1.2% (1/84) versus 1.7% (3/174) in blood donors (8). The discrepant results between the two studies might be due to methodological differences and the composition of the haemophilic patient group. Whilst an immunofluorescence assay with stimulated HHV-8-infected BCBL cells (native antigens) was used for the first study, and 7.2% of individuals of the haemophilic group were HIV-infected, the second study was done by an enzyme immunoassay with recombinantly expressed HHV-8 protein, and includes one-third of HIV-infected haemophiliacs. In view of these findings, we decided to investigate the HHV-8 infection profile in our local haemophilic group by measurement of HHV-8 antibodies and DNA.

We tested 120 sera from the same number of male haemophiliacs (111 cases of haemophilia A, 8 of haemophilia B, 1 case of von Willebrand’s disease), of whom 60 were HIV-infected. All HIV-infected haemophiliacs except one, and 41 of the 60 non-HIV-infected haemophiliacs suffered from severe coagulopathy. All haemophiliacs received non-virus-inactivated concentrates in the era before routine viral inactivation, i.e. when the risk for viral contamination of the coagulation factor concentrates was high. In addition, sera from 75 medical staff members and students, and from 11 homosexual men with HIV-associated KS were examined.

HHV-8 immunofluorescence assay was done with phorbol ester-stimulated BCBL-1 cells. Sera were diluted 1:20, 1:50, and 1:100, resp. Sera with clear reactivity at the 1:50 dilution were considered positive. Sera positive at the 1:100 dilution were titrated in 3-fold dilutions to determine end-point titers. No serum specimen showed non-specific