Inhibitors of Coagulation in Terminal Renal Failure and during Hemodialysis

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Dear Sir,

The paradoxical occurrence of both bleeding tendency and thrombotic complications in advanced renal failure is still an enigma and, therefore, a problem of continued interest. Hemostatic alterations in renal failure are certainly complex and involve abnormal platelet function [1], increased release of vascular prostacyclin [2], impaired release of plasminogen activator [3], and abnormalities in Factor V^{III}-von Willebrand complex [4]. Low levels of circulating antithrombin III (AT III) have also been reported [1].

Recently, Alegre et al. [5] reported a decrease in im-munoreactive protein C during hemodialysis and suggested that this may contribute to the prothrombotic state observed in these patients.

As a part of a continued research program dealing with the hemostasis in uremia, we have investigated im-munoreactive protein C and protein C activity in patients with progressive renal failure, patients on hemodialysis, and healthy controls.

Protein C antigen was measured by Laurell rocket immunoelectrophoresis, the protein C activity was determined according to Francis and Patch, with a pool of plasma from 30 healthy males used as calibrant in both assays, as previously described in detail [6]. We studied 14 hemodialysis patients and 21 healthy controls. Values before and after hemodialysis were compared with Wil-coxon's test of paired differences. Values from patients and controls were further compared with the Mann-Whitney test. The results are summarized in table I.

Table I. Plasma protein C antigen levels and activity (arbitrary units) in 21 healthy controls and 14 hemodialysis patients before and after dialysis

Immunoreactive protein C was normal both before and after hemodialysis. In contrast, protein C activity was depressed both before and after hemodialysis ($p < 0.01$), although the activity increased after dialysis compared with predialysis values ($p < 0.01$). Only a minor, however significant, increase in immunoreactive protein C was noticed in the present study during dialysis ($p < 0.02$).

The present results confirm and extend our previous findings regarding changes in immunoreactive protein C and protein C activity in renal failure and during hemodialysis [6, 7]. We have earlier found a decreasing protein C activity with progressive renal failure [7] and a low activity, despite normal antigen levels, in hemodialysis patients [6], pointing to the existence of a

hitherto unknown inhibitor of protein C in uremic plasma. Our results further suggest that this inhibitor may be removed, at last partly, by hemodialysis.

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Alegre et al. [5] observed a decrease in immunoreactive protein C during hemodialysis. This is in contrast to our finding of a minor increase in protein C antigen levels during hemodialysis – an alteration which undoubtedly reflects hemoconcentration during the treatment.

Similarly, Alegre et al. [5] noticed a decrease in immunoreactive AT III immediately after hemodialysis. This is also in contrast to our reports of unchanged immunoreactive AT III and AT III activity during hemodialysis using several different hemodialysis membranes [8]. The reasons for these conflicting findings are not readily apparent, but our results are supported by other investigators [9].

In summary, our findings document a decreased protein C activity, despite normal antigen levels, in advanced renal failure which should be added to the list of hemostatic abnormalities afflicting these patients. A dialyzable inhibitor impairing protein C activity or causing a defect in its dicarboxylation is the most probable cause, but final elucidation of its nature awaits further studies.

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