PART III

DIALYSIS 1

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          D Fries

PART IV

DIALYSIS 2

Chairmen: N K Man
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PART V

DIALYSIS AND HAEMOFILTRATION

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PART VI

PERITONEAL DIALYSIS

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PROSTACYCLIN PREVENTS ENDOTHELIAL AND PLATELET DAMAGE DURING DIALYSIS

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Introduction

EDTA Registry figures [1] show that patients receiving all forms of renal replacement therapy suffer a greatly increased mortality from cardiovascular disorders compared with the normal population and, further, that this increased mortality is largely due to the greatly elevated risk of fatal myocardial infarction and cerebrovascular accident in haemodialysis patients. We have previously suggested an hypothesis [2] that might resolve the apparently anomalous coexistence of a high incidence of atherosclerotic cardiovascular disease with the characteristic uraemic haemorrhagic diathesis, which might be expected to confer some protection from atherogenesis (Figure 1). The central tenet of this hypothesis is that uraemia and its associated cardiovascular risk-factors induce continuous low grade intravascular coagulation and platelet activation. These result in vascular endothelial damage, the inevitable consequence of which is atheroma. The reinfusion of platelets and other factors activated by the extracorporeal circulation of blood during haemodialysis may exacerbate this situation and increase endothelial damage and its consequences. This paper summarises our evidence that haemodialysis can induce both platelet and endothelial damage which can be prevented by the administration of prostacyclin.

Patients and Methods

Twenty-two patients were studied, all had been on regular dialysis therapy for at least 6 months, using flat-bed dialysers with cuprophane membranes (Kii or Gambro). Heparin from the same batch was administered as an intravenous bolus of 50IU/kg at the start of dialysis, or as a constant infusion of 30IU/kg/hour for the first 4 hours of a 5 hour dialysis. Prostacyclin (formulated by Wellcome Research Laboratories and synthesised by Upjohn) was administered as a continuous infusion of 5ng/kg/minute throughout dialysis. Arterial blood samples were obtained from the dialyser inlet for platelet count, β-thromboglobulin radioimmunoassay, factor VIII-related antigen (VIII-RA) immunoelectrophoresis, and anti-
thrombin III (AT III) which was measured as total rate-independent antithrombin activity in excess heparin [3].

The response of AT III to heparin and to dialysis was studied in four groups
of RDT patients. Each received 50IU/kg heparin as a bolus. Group 1 were not dialysed. Group 2 were dialysed. Group 3 also underwent haemodialysis, but also received heparin as an infusion of 30IU/kg/hour. Group 4 received prostacyclin 5ng/kg/minute during haemodialysis.

Results

Dialysis with heparin alone induced a fall in the platelet count, which tended to be restored towards the end of dialysis (Table I). When prostacyclin was administered in addition to heparin, the platelet count remained stable or even rose during dialysis. β-thromboglobulin levels rose progressively throughout dialysis with heparin, but were unchanged when prostacyclin was also administered. Factor VIII-related antigen also rose progressively throughout routine dialysis to a peak of 131.3% ± 7.7 SGM of the initial value (p < 0.001). In contrast, the administration of additional prostacyclin prevented this rise, the level of VIII-RA remaining unchanged throughout dialysis.

Table I. Changes in platelet and coagulation parameters during haemodialysis with and without additional prostacyclin

<table>
<thead>
<tr>
<th>Dialysis duration (mins)</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet - Heparin</td>
<td>86 ± 4</td>
<td>92 ± 4</td>
<td>89 ± 4</td>
<td>95 ± 5</td>
<td>98 ± 7</td>
</tr>
<tr>
<td>Count Heparin + PGI</td>
<td>99 ± 2</td>
<td>98 ± 4</td>
<td>103 ± 4</td>
<td>106 ± 4</td>
<td>107 ± 4</td>
</tr>
<tr>
<td>βTG - Heparin</td>
<td>111 ± 5</td>
<td>120 ± 5</td>
<td>126 ± 6</td>
<td>138 ± 5</td>
<td>145 ± 8</td>
</tr>
<tr>
<td>- Hep + PGI</td>
<td>100 ± 5</td>
<td>97 ± 7</td>
<td>99 ± 6</td>
<td>106 ± 8</td>
<td>102 ± 7</td>
</tr>
<tr>
<td>VIII-RA - Heparin</td>
<td>103 ± 3</td>
<td>114 ± 9</td>
<td>121 ± 8</td>
<td>123 ± 9</td>
<td>131 ± 15</td>
</tr>
<tr>
<td>- Hep + PGI</td>
<td>99 ± 2</td>
<td>101 ± 3</td>
<td>101 ± 3</td>
<td>102 ± 9</td>
<td>105 ± 6</td>
</tr>
<tr>
<td>AT III - Heparin</td>
<td>112 ± 4</td>
<td>124 ± 5</td>
<td>130 ± 5</td>
<td>138 ± 1</td>
<td>153 ± 2</td>
</tr>
<tr>
<td>- Hep + PGI</td>
<td>97 ± 2</td>
<td>101 ± 3</td>
<td>102 ± 2</td>
<td>105 ± 4</td>
<td>103 ± 3</td>
</tr>
</tbody>
</table>

Results are expressed as mean percent ± SEM of pre-dialysis values. The change in all values during dialysis with heparin alone was significant (p < 0.005, or better). The difference in values during dialysis with and without prostacyclin was also significant (p < 0.01 or better). PGI = prostacyclin; βTG = β-thromboglobulin; VIII-RA = factor VIII-related antigen; AT III = antithrombin III

Uraemia patients respond to bolus heparin in the same way as normals (Figure 2), with a reduction in plasma AT III levels and a subsequent return to baseline levels after about 90 minutes. The mechanism of this fall and subsequent restoration in AT III levels is unclear but may result from sequestration of heparin/AT III complexes. However, when bolus heparin is immediately followed by haemodialysis (Group 2), this fall in AT III is abolished and there is instead a progressive rise throughout the period of study. That this is an effect of haemodialysis rather than a response to heparin is shown by Group 3 who received heparin as both a bolus and an infusion. In this group there was a parallel rise in AT III
which persisted even after the heparin infusion had ceased after 4 hours of the 5 hour dialysis. In fact there is no correlation between heparin levels or anticoagulant effect and AT III levels during haemodialysis [4]. In contrast, there is no change in AT III levels during dialysis with additional prostacyclin.

Discussion

These results confirm and extend our previous observations [5,6] that prostacyclin prevents the platelet consumption and activation which occur during routine haemodialysis with heparin anticoagulation. Platelet activation continues after the nadir of the thrombocytopenia, as shown by the progressive rise in β-thromboglobulin, which is a specific factor released from activated platelets. Protection of platelets from activation by dialysis can also be demonstrated by the heparin-sparing effect of prostacyclin, which presumably results from the inhibition of release of platelet heparin-neutralising activity [5]. The reinfusion of platelet aggregates and activated platelets may contribute to the vascular damage induced by haemodialysis and can be prevented by the use of prostacyclin.

Antithrombin III, the endogenous heparin cofactor, is not only a circulating protein but also adheres to both platelets and vascular endothelium [7]. However, it is only detached from platelets when they are disrupted, for example by sonication. We suggest that the heparin-independent rise in AT III during haemodialysis results from its detachment from the vascular endothelium which is damaged by the reinfusion into the patient of platelets and other blood components which have been activated by contact with the artificial surface of the dialyser. Prostacyclin prevents this rise in AT III and, as it has no direct interaction with either AT III or its assay, we presume that this indicates the vascular endothelial protective effect of prostacyclin.
Factor VIII-related antigen is synthesised by vascular endothelium [8] and is released by vascular injury. Therefore, the response of VIII-RA to haemodialysis must result from acute vascular endothelial damage. The prevention of the rise in VIII-RA by prostacyclin may result from either a direct vascular protective effect or from inhibition of platelet aggregation and activation by the dialyser. The progressive rise in AT III and VIII-RA throughout haemodialysis indicate acute injury to the vascular endothelium which can be prevented by the administration of the potent antiplatelet agent, prostacyclin.

Furthermore, the release of factor VIII during dialysis may further exacerbate the continuous low grade intravascular coagulation which occurs in patients on regular dialysis therapy [2]. We have demonstrated that prostacyclin prevents the damage to platelets and blood vessels which occurs during routine haemodialysis with heparin and which may contribute to the high risk of atherosclerotic cardiovascular disease observed in the dialysis population (Figure 1). It may be that the regular use of platelet suppressive therapy during haemodialysis will reduce the incidence of cardiovascular mortality and thrombotic complications in patients on regular dialysis therapy.

References

1 Brunner FP et al. Proc EDTA 1979; 16: 4
5 Turney JH et al. Lancet 1980; ii: 219
6 Turney JH et al. Proc EDTA 1980. 17: 318
7 Chan V, Chan TK. Thrombosis Res 1979; 15: 209
8 Bloom AL, Peake IR. Br Med Bull 1977; 33: 219

Open Discussion

FARREL (Sydney) What were the loading doses of heparin and the continuous infusion rates? Do you believe that the amount of heparin can in fact influence the levels of some of these parameters?

TURNENY In all studies we used our standard loading dose which was 50IU/kg. When an infusion was used we used 30 units/kg/hour. In each study all the heparin came from the same batch. Heparin is very complex as you know and obviously the dose and the type and the batch of heparin may alter the response of platelets and other things but as we summarise five or six different studies, each using different types of heparin and each giving very similar results, I think that the response is largely to the dialyser rather than to heparin as illustrated by AT III and factor VIII.

FARRELL We have actually been using heparin modelling and I think this is probably a more sensible approach; that is to give the dose that the patient
requires. We found that in fact the platelet factor IV levels and the β-thromboglobulin levels were more related to the loading dose of heparin and were much less dependent on the dialyser. We also did not see any thrombocytopenia.

DI GIULIO (Paris) Glycosaminoglycans are increased in uraemia and heparin itself can be considered as a glycosaminoglycan. One of the main functions of glycosaminoglycans is the binding of low density lipoprotein to the endothelial wall. Do you think that it is possible to differentiate between the action of heparin and that of the increased level of endogenous glycosaminoglycans on the endothelial wall?

TURNEY We think our evidence from these coagulation factors shows that the response in AT III and factor VIII is independent of heparin because you lose relationships that you previously had with heparin as a result of the dialysis. Heparin's effects on lipids or free fatty acids etc., are complex and we have not studied these at all.