HAEMODIALYSIS WITH PROSTACYCLIN (EPOPROSTENOL) ALONE

P B Rylance, M P Gordge, *H Ireland, *D A Lane, M J Weston

Dulwich Hospital, *Charing Cross Hospital Medical School, London, United Kingdom

Summary

Dialysis with prostacyclin (Epoprostenol, PGI₂) alone prevents platelet activation and endothelial cell stimulation but not the elevation of fibrinopeptide A (FPA), a sensitive marker of fibrin generation. The generation of FPA may explain why some patients develop clot in the dialysis circuit during PGI₂-only dialysis. In combination with heparin, PGI₂ augments the anticoagulant effect of the heparin as well as providing platelet protection.

Introduction

Patients with chronic renal failure may display a divergence of normal haemostasis with not only a high prevalence of cardiovascular mortality but also a bleeding tendency. Platelet dysfunction may contribute to this bleeding tendency and may be made worse by both functional exhaustion of platelets (due to their activation on the dialysis membrane), and by heparinisation. Reversible protection of platelets may be obtained during haemodialysis by PGI₂ infusion [1], and may minimise risk of bleeding. Patients may be dialysed with PGI₂ alone [2–4] though with increased experience with PGI₂, it has become clear that in some patients fibrin may form resulting in clotting in the dialysis circuit. This study was undertaken to elucidate further the behaviour of platelets and clotting parameters during dialysis with PGI₂.

Patients and methods

In eight stable chronic haemodialysis patients a single dialysis with PGI₂ alone (Epoprostenol, Wellcome) was compared with a dialysis with unfractionated heparin. PGI₂ (0.5mg diluted in 50ml glycine buffer, pH 10.5) was infused into a peripheral vein via an electrically-driven syringe pump at a rate of 5ng/kg/min. Following the commencement of dialysis, the PGI₂ infusion was transferred to the arterial inlet of the dialyser and subsequently the dose was
increased provided the blood pressure did not significantly fall (2.5–10ng/kg/min, mean 6.9 ± 0.6ng/kg/min). In the dialysis with heparin, a bolus of 50iu/kg (Leo) was given into the arterial line at the start of dialysis and after two hours an infusion of 30iu/kg/hr was continued to the end of dialysis. All dialyses lasted for four hours and were carried out with flat-plate cuprophan dialysers (Gambro). Blood samples, withdrawn slowly from the arterial line, were taken pre-PGI₂ infusion, pre-dialysis (0 min), 15 min, 60 min, 120 min and 240 min, for platelet count, activated whole blood clotting time (AWBCT, measured by the Hemochron technique), activated partial thromboplastin time (APTT), fibrinopeptide A (FPA, the first peptide cleaved by thrombin from the N-terminus of fibrinogen, and cleavage of FPA signals the formation of fibrin-1), β-thromboglobulin (βTG) and platelet factor 4 (PF4) (both factors released from platelet α granules following activation), and factor VIII related antigen (VIII RAg, a marker of endothelial cell stimulation). Platelet aggregation (maximum) was measured in response to ADP (5μmol) and collagen (1μg/ml) within two minutes of blood sampling, using an electronic impedance whole blood aggregometer. The remaining samples were kept on melting ice, centrifuged at 4°C and stored at −20°C for subsequent analysis. FPA, βTG and PF4 were measured by radioimmunoassay techniques and VIII RAg by radial immunodiffusion. Where values are expressed as per cent changes, pre-dialysis = 100 per cent. Results are expressed as mean ± standard error of mean. Statistical comparisons were made within and between regimes by paired Student’s ‘t’ tests.

In a separate study a further eight haemodialysis patients were dialysed with bolus doses of heparin (Leo) 50iu/kg, 30 iu/kg and 20iu/kg given at the commencement of successive dialyses and studied for two hours. The same patients were subsequently dialysed on three further occasions with the same heparin boluses but with the addition of PGI₂ infusion (5ng/kg/min). In this second study the prolongation of thrombin clotting time (TCT) at 15 minutes was plotted against the bolus dose of heparin with and without PGI₂ infusion. FPA was measured during both dialyses with heparin alone and with PGI₂ + heparin, and the correlation between FPA and AWBCT was plotted for PGI₂ + heparin dialysis.

Results

PGI₂ was well tolerated; initial mild facial flushing was transient and at 5ng/kg/min patients experienced no other side effects or significant hypotension compared with heparin dialysis. The results of the first study are shown in Figure 1. During dialysis with PGI₂ there was a small but not significant fall in AWBCT; mean APTT significantly fell at 15 minutes and remained less than pre-dialysis values. Platelet count fell by nine per cent though this was not significantly different from heparin dialysis. βTG rose during heparin dialysis, while with PGI₂ βTG was significantly lower but was significantly elevated above predialysis values at four hours. PF4 was not significantly changed during PGI₂ dialysis, while PF4 with heparin dialysis was markedly elevated at 15 minutes, probably as a result of heparin displacing PF4 from the vascular endothelium. Whereas VIII RAg rose with heparin dialysis, with PGI₂ dialysis there was no
Figure 1. Platelet and clotting parameters during haemodialysis with PGI₂ alone (●--●) compared with dialysis with heparin alone (○--○)
significant rise. PGI₂ pre-infusion reduced platelet aggregation by collagen by 64.7 ± 11.7 per cent and by ADP by 76.4 ± 8.4 per cent and did not change further during the dialysis. The half life of platelet inhibition by PGI₂ in ex-vivo blood samples was 32 minutes. With heparin dialysis platelet aggregation became progressively depressed to a maximum of 54.8 ± 11.8 per cent with collagen and 25.3 ± 27.6 per cent with ADP at 240 minutes. In the heparin dialysis, in two patients the heparin regime used was not adequate to prevent rise of FPA. During PGI₂ dialysis FPA levels were markedly elevated and were significantly higher than heparin dialysis. In three patients sufficient clots formed in the venous trap during PGI₂ dialysis to require the addition of small heparin boluses (500–1000iu) at 60 mins, 120 mins and 180 mins respectively.

In the second study combining heparin with PGI₂, elevation of βTG and VIII RAg was again prevented by the addition of PGI₂. TCT was prolonged at 15 minutes by PGI₂ equivalent to an effective increase of heparinisation of 50 per cent with the 20iu/kg bolus and 54 per cent with the 30iu/kg bolus (Figure 2). There was no significant rise of FPA with the 50 iu/kg bolus both with heparin-only and with PGI₂ + heparin during two hours of dialysis. With the 30iu/kg heparin-only dialysis, FPA was significantly elevated at 60 minutes compared with pre-dialysis values (0 min = 6.7 ± 1.1 ng/ml, 60 min = 15.0 ± 4.1, p<0.05). With PGI₂ heparin dialysis, FPA at 60 minutes (8.9 ± 2.1 ng/ml) was significantly less than heparin-only dialysis (p = 0.05), and elevation of FPA above pre-dialysis values was delayed by PGI₂ until 120 minutes (15.0 ± 1.2, p<0.05). With the 20iu/kg bolus the AWBCT returned to pre-dialysis values by 60 minutes with both heparin and PGI₂ + heparin dialysis and FPA was elevated with both. There was a significant negative linear correlation between AWBCT and FPA (log transformed data) (r = -0.59, p<0.001) and FPA did not rise above the upper limit of pre-dialysis values (11.2 ng/ml), as long as AWBCT was prolonged 20 per cent above pre-dialysis values.

Discussion

Conventional haemodialysis with heparin results in platelet activation as shown by the elevation of βTG, and stimulation of endothelial cells as reflected by the rise of VIII RAg. We have shown that dialysis with PGI₂ results in platelet and endothelial protection, as does dialysis with a combination of heparin + PGI₂. PGI₂ at the doses used in this study results in almost complete inactivation of platelets which is quickly reversible. PGI₂-only dialysis does not however guarantee adequate anticoagulation as judged by generation of FPA, and in some patients sufficient clot developed to require the addition of heparin. When PGI₂ and heparin are used together during haemodialysis, PGI₂ potentiates the anticoagulant activity of heparin by approximately 50 per cent, possibly by reducing heparin-neutralising activity release from platelets when they are activated by the dialyser membrane. The second study showed a significant reduction in generation of FPA when PGI₂ was infused with heparin, providing confirmation of the heparin-inhibiting effects of PGI₂. If AWBCT is maintained at 20 per cent above pre-dialysis values by small heparin boluses, FPA levels are not elevated above the upper limit of pre-dialysis values. Thus for a
Figure 2. Relationship between prolongation of thrombin clotting time (TCT) at 15 minutes during dialysis with a combination of PGI₂ and heparin (•—•) compared with dialysis with heparin alone (○—○)

Patient at risk of haemorrhage, PGI₂ can be used to protect platelets from activation and to reduce heparin requirements as judged by TCT and FPA. Elsewhere we report our experience of 101 dialyses with PGI₂ in patients who were actively bleeding or were at risk of doing so [5]. In none of these did bleeding appear to be aggravated during or after the dialysis but in 30 per cent of dialyses with PGI₂-alone there was significant clotting in the dialyser requiring changing of bubble-trap or circuit and heparinisation. The results of these studies suggest that for dialysis in patients at risk of bleeding it is preferable to combine prostacyclin infusion with small doses of heparin the activity of which is enhanced by PGI₂, to prevent fibrin generation and dialyser clotting.
References

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