EVALUATION OF PROSTAGLANDIN D$_2$ (PGD$_2$) AS AN ANTICOAGULATIVE AGENT FOR HAEMODIALYSIS IN COMPARISON WITH PROSTAGLANDIN E$_1$ (PGE$_1$)

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Summary

Prostaglandin D$_2$ (PGD$_2$), a potent antiplatelet agent, was evaluated as an antithrombotic agent for haemodialysis in comparison with prostaglandin E$_1$ (PGE$_1$) and prostaglandin I$_2$ (PGI$_2$).

When antiplatelet action was evaluated, taking the degree of associated hypotension into consideration, PGD$_2$ was found to be superior to PGE$_1$ and PGI$_2$ as the latter two had the negative effect of inducing hypotension, while PGD$_2$ had a less hypotensive effect.

The suppression of the platelet function by PGD$_2$ was observed to have only a slight influence on platelet function in systemic blood.

Introduction

It is widely acknowledged that the platelet and intrinsic coagulation system is activated in extracorporeal circulation. Heparin is currently the sole antithrombotic agent that can be used for the purpose of inhibiting the accompanying coagulation.

Several authors [1, 2] have reported that PGI$_2$ is an effective antithrombotic agent for haemodialysis, suggesting the importance of inhibiting platelet function during extracorporeal circulation. However, since PGI$_2$ also has a potent hypotensive action it is not clinically practical.

We have studied the possibility of using PGD$_2$ as an antithrombotic agent for haemodialysis in comparison with PGE$_1$ and PGI$_2$, as the hypotensive action of PGD$_2$ is weak while its antiplatelet action is between that of PGE$_1$ and PGI$_2$.

Materials and methods

1. The inhibitory effects of PGD$_2$, PGE$_1$ and PGI$_2$ on platelet aggregability were evaluated in healthy volunteers. Platelet aggregability was assessed by Born’s
method [3] using the Sienco Dual Sample Aggregation Meter with ADP (Sigma) at the concentration of 6μM, and collagen (Hormone Chemie) at 4.5mg/ml.

2. Doses of PGE$_1$, PGD$_2$ and PGI$_2$ enough to reduce diastolic pressure by 10mmHg were determined in the same volunteers.

The administration of these prostaglandins were started from doses of 32, 128 and 2ng/kg/min, respectively. The doses were doubled until a 10mmHg reduction of diastolic pressure was achieved. Blood pressure was checked every 5 minutes.

3. Platelet aggregability was assessed in the blood samples collected just before and after the dialyser 10 minutes after the start of haemodialysis.

Pre- and post-dialysis platelet aggregability was also assessed in five patients undergoing haemodialysis with the simultaneous infusion of PGD$_2$ and heparin at the rate of 100μg/hr and 1,000U/hr, respectively.

The concentrations of reagents were varied individually, due to the fact that concentrations necessary to detect the change of platelet aggregability differed from patient to patient.

4. The doses of PGE$_1$ and PGD$_2$ which produced adverse effects during haemodialysis were investigated in uraemic patients on regular dialysis treatment.

The administration of PGE$_1$ and PGD$_2$ was started at 25 and 50μg/hr, respectively, and increased by 25μg/hr with every dialysis. The infusion was immediately discontinued at the appearance of side effects such as hypotension, nausea, and headache. The dose at this point was determined as the critical dose at which side effects were induced. Side effects disappeared after the discontinuance of the infusion.

Results

1. As shown in Figure 1, the inhibitory effect of 1ng/ml PGI$_2$ on ADP-induced platelet aggregability was equal to those of 8–16ng/ml PGD$_2$ and 16–32ng/ml PGE$_1$. Results with respect to collagen-induced aggregability were similar.

2. A 10mmHg reduction in diastolic blood pressure was achieved at infusion rates of 8ng/kg/min PGI$_2$, 512ng/kg/min PGD$_2$, and 128ng/kg/min PGE$_1$. Thus, the hypotensive action of PGI$_2$ is 16 times that of PGE$_1$, and 64 times that of PGD$_2$.

Antiplatelet action of PGD$_2$ was one-eighth to one-sixteenth that of PGI$_2$. When the hypotensive action described above and this antiplatelet action are considered together, it can be stated that the effectiveness of PGD$_2$ as an anticoagulant agent for haemodialysis is four to eight times greater than that of PGI$_2$. When these two actions are considered with respect to PGE$_1$, the clinical usefulness is almost the same as that of PGI$_2$.

3. Maximum collagen-induced platelet aggregability was suppressed by PGD$_2$, as aggregability was 61% before and 34% after the infusion line for PGD$_2$. The same tendency was observed in ADP-induced aggregability: 50% before and 9% after
Figure 1. The effects of prostaglandin $I_2$, $D_2$ and $E_1$ on platelet aggregability induced by ADP (6μM)

TABLE I. The effect of haemodialysis with prostaglandin $D_2$ on platelet aggregability in systemic blood

<table>
<thead>
<tr>
<th>Patient number</th>
<th>PGD$_2$ (ng/kg/min)</th>
<th>ADP-induced aggregability (%)</th>
<th>Collagen-induced aggregability (%)</th>
<th>Mean ± SD</th>
<th>Pre HD</th>
<th>Post HD</th>
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Mean ± SD | 64±13 | 53±18 | 57±23 | 50±21* |

* p < 0.05 vs Pre HD

Figure 2. Threshold to initiate adverse effects (hypotension, nausea, etc.) of prostaglandin $E_1$ (PGE$_1$) and prostaglandin $D_2$ (PGD$_2$) during haemodialysis
the line. No improvement of the platelet aggregability was observed in the blood collected after the dialyser, suggesting that PGD₂ is non-dialysable.

4. After the termination of haemodialysis with PGD₂ infusion, it was observed that platelet aggregability was slightly suppressed. The suppressive effect was more significant in ADP-induced aggregability (Table 1). The influence on systemic blood was slight.

5. The critical dose at which side effects are induced were 17.5 ± 6.3ng/kg/min for PGE₁, and 36.4 ± 7.5ng/kg/min for PGD₂ (Figure 2).

Discussion

Platelets play an important role in the coagulative process in extracorporeal circulation. The reports by Woods et al [1] and Zusman et al [2], which describe successful anticoagulation in haemodialysis by PGI₂ alone as an antithrombotic agent, serve as evidence of the importance of platelet inhibition in managing extracorporeal circulation. However, PGI₂ has a potent vasodilating and hypotensive action. The concentrations necessary to show antiplatelet action and vasodilating action are similar. Accordingly, should one use PGI₂ to obtain adequate antiplatelet activity, the appearance of adverse hypotension is an inevitable outcome.

Patients on haemodialysis are very sensitive to these kinds of hypotensive agents. In fact, PGE₁ can induce hypotension in a normotensive person at the infusion rate of 100ng/kg/min [4], while only 17.5ng/kg/min has the same effect in dialysis patients during haemodialysis. When the patients were off dialysis, however, their hypotensive reaction to PGE₁ was almost the same as that of normal persons. Therefore, the sensitivity to prostaglandins on the part of haemodialysis patients derives from haemodynamic factors during dialysis. The vasodilating effect of prostaglandins as an anticoagulative agent therefore poses a problem.

Although PGE₁ and PGI₂ show a potent antiplatelet action, they are not practical agents for haemodialysis because of their hypotensive effect. On the other hand, PGD₂ is far superior to PGI₂ from a clinical standpoint because its antiplatelet action is more selective than that of PGE₁ and PGI₂. The different selectivities in antiplatelet action among the three prostaglandins seem to reflect differences in receptors, since the receptor of PGD₂ is different from that of PGE₁ and PGI₂ [5, 6].

The infusion of PGD₂ at the rate of 100µg/hr had an inhibitory effect on platelet function in extracorporeal circulation without inducing a fall in blood pressure. There was no change in inhibitory effects on platelet aggregability between the inlet and outlet of the dialyser, suggesting the non-dialysability of PGD₂. Since the molecular weight of PGD₂ is 351, PGD₂ is suspected to be protein-bound or bound to the surface of blood cells. Despite this non-dialysability of PGD₂, its influence on platelet aggregability in systemic blood was clinically negligible at the dose administered in the present study. This is partly because of the dilutional effect of systemic blood and also due to the inactivation of PGD₂.
in the lung, similar to PGE₁ [7].

In conclusion, PGD₂ appears the best antithrombotic agent among currently available prostaglandins when used for haemodialysis.

References

3 Born GVR. *Nature* 1962; 194: 927
5 Whittle BJR, Moncada S, Vane JR. *Prostaglandins* 1978; 16: 373

Open Discussion

BOEN (Amsterdam) How do you explain the increase in clearance during dialysis?

NAKAGAWA The reason why the PGD₂ improves the reduction of urea clearance which was observed in heparin dialysis is the effect on the adhesion and aggregation of platelets on the membrane.