Increased production of prostacyclin after injury to the microvasculature in uraemic patients

W. SLAZUS

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Summary

It is well known that uraemia is associated with a bleeding tendency. The incidence of dangerous bleeding episodes has decreased since the introduction of dialysis, but is still a problem for patients needing major surgical procedures or diagnostic biopsies of, for instance, the kidney or liver.1

A prolonged bleeding time is still the best, although it is not infallible, indicator of a clinical bleeding tendency.2 Various aetiological factors have been proposed to explain this defect, e.g. a low packed-cell volume (PCV);3,4 decreased in vitro platelet aggregation;5 decreased thromboxane A₂ (TXA₂) production by platelets;6 increased prostacyclin (PGL) production by endothelial cells;7 abnormalities of von Willebrand factor8,9 and parathyroid hormone;10 and abnormal platelet surface carbohydrates.11 Conflicting results are regularly published6,12-15 and the true pathogenesis of this defect of primary haemostasis is still unresolved.

A new experimental approach to the evaluation of primary haemostasis has recently been published.6,10 Blood collected from cuts made for measurement of bleeding time, a standardised injury of the microvasculature, is used for the measurement of different mediators operative in haemostasis, e.g. thromboxane B₂ (TXB₂) — as an end-product of platelet cyclo-oxygenase activity — and 6-keto-prostaglandin F₁α (6KPGF) — as an indicator of vascular endothelial synthesis of PGI₁.

In the present study in vivo production of TXA₂ by platelets and PGL by vascular endothelium was examined in patients with severe chronic renal failure and compared with normal controls.

Patients and methods

The protocol was approved by the Ethical Committee of the Medical Faculty, University of Stellenbosch, and informed consent was obtained from all patients. Ten patients, 8 men and 2 women, with severe chronic renal failure (serum creatinine value over 160 μmol/l or receiving regular haemodialysis) were examined. Patients on haemodialysis were examined immediately before a dialysis session. No diabetics, patients with nephrotic syndrome or patients receiving drugs that could influence prostaglandin metabolism were included in the study. No patient received recombinant human erythropoietin.

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Patients and methods

The protocol was approved by the Ethical Committee of the Medical Faculty, University of Stellenbosch, and informal consent was obtained from all patients. Ten patients, 8 men and 2 women, with severe chronic renal failure (serum creatinine value over 600 μmol/l or receiving regular haemodialysis) were examined. Patients on haemodialysis were examined immediately before a dialysis session. No diabetics, patients with nephrotic syndrome or patients receiving drugs that could influence prostaglandin metabolism were included in the study. No patient received recombinant human erythropoietin.

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TABLE I.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>TXB2 (pg/ml)</th>
<th>6KPGF (pg/ml)</th>
<th>Haemoglobin (g/l)</th>
<th>Platelet count (x 10^9)</th>
<th>Bleeding time (min)</th>
<th>TXB2 (pg/ml)</th>
<th>6KPGF (pg/ml)</th>
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<tbody>
<tr>
<td>1</td>
<td>1 010.9</td>
<td>53.8</td>
<td>38.9</td>
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<td>679.3</td>
<td>71.7</td>
<td>71</td>
<td>141</td>
<td>&gt; 12</td>
<td>373.1</td>
<td>16.2</td>
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<td>3</td>
<td>407.1</td>
<td>81.9</td>
<td>48</td>
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<td>&gt; 12</td>
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<tr>
<td>4</td>
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<td>86.5</td>
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<td>394</td>
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<td>1 148.3</td>
<td>21.4</td>
</tr>
<tr>
<td>5</td>
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<td>84.6</td>
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<td>27.4</td>
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<td>6</td>
<td>1 758.1</td>
<td>45.2</td>
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<td>251</td>
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<td>636.9</td>
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<tr>
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<td>654.1</td>
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<tr>
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<td>37.1</td>
<td>64</td>
<td>207</td>
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<td>51.7</td>
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<td>42.7</td>
<td>102</td>
<td>268</td>
<td>9</td>
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<td>67.1</td>
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<tr>
<td>10</td>
<td>846.9</td>
<td>64.1</td>
<td>93</td>
<td>258</td>
<td>7</td>
<td>652.9</td>
<td>55.1</td>
</tr>
<tr>
<td>Mean</td>
<td>851.7±371.0</td>
<td>59.9±21.7</td>
<td>73.9±20.5</td>
<td>259±121</td>
<td>668.4±292.9</td>
<td>37.3±18.3</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05.

other 4 patients. All the controls had bleeding times that were within normal limits.

TXB2 and 6KPGF in blood from bleeding time cuts (Table I)

In the controls 668.4 ± 292.9 pg/ml TXB2 and 37.3 ± 18.3 pg/ml 6KPGF was measured in blood collected over the whole duration of the bleeding time. The amount of TXB2 measured in uraemic patients (851.7 ± 371.0 pg/ml) did not differ significantly from that of the controls (P > 0.05). The production of 6KPGF was, however, increased by 59% in uraemic patients (59.3 ± 21.7 pg/ml) compared with controls and this difference was statistically significant (P < 0.05). The TXB2/6KPGF ratio did not differ significantly between the patient (17.4) and the control (23.5) group. There was no significant correlation between haemoglobin levels, bleeding times, platelet counts and either TXB2 or 6KPGF levels. Because of the small number of patients in the study, this cannot be regarded as absolute proof of non-correlation.

Discussion

Prostaglandin metabolites of the cyclo-oxygenase pathway play a very important role in the aggregation of platelets. TXA2 is strongly stimulatory1213 and PGI2 strongly inhibitory14 to platelet aggregation. Both have short half-lives in vivo and the stable breakdown products TXB2 and 6KPGF are measured in vivo as an indication of in vivo production.

It has recently been shown that the measurement of different mediators of haemostasis in blood collected from bleeding-time cuts is an excellent method for in vivo evaluation of the primary haemostatic mechanism.15,16 These measurements are indicative of events at the level of the primary haemostatic mechanism and, unlike measurements of TXB2 and 6KPGF in venous blood or urine, are not an indication of production in the whole vascular system and other sources, e.g. the kidneys.

Results of in vitro experiments, e.g. the determination of PGI2 production by isolated vascular tissue of uraemic patients, should be verified, if possible, by in vivo methods, e.g. as used in the present study. The in vitro method is also sensitive to abnormal cyclo-oxygenase activity, as has been shown by measurement of TXB2 after treatment with low dose aspirin.17

The results of the present study are an indication that in vivo production of TXA2 by uraemic platelets is not reduced in comparison with normal controls. In patients on maintenance haemodialysis specimens were obtained immediately before the next dialysis and platelet activation during dialysis could thus not account for the failure to demonstrate decreased production of TXB2. The presence of a functional cyclo-oxygenase defect, one of the proposed mechanisms of the uraemic bleeding tendency, could thus not be confirmed by this in vivo evaluation.

The production of PGI2 by injured vascular endothelial cells of uraemic patients is, however, significantly increased. The above findings confirm the results of Kyrie et al.18 who used a similar method of investigation. The lower TXB2/6KPGF ratio in the patients, in spite of higher levels of TXB2 than the controls, also suggests that the increased PGI2 levels are more important than the increase in production of TXA2.

The cause of the increased production of prostacyclin has not been determined. It has been shown that normal platelet-poor plasma contains a factor that causes release of prostacyclin from vascular endothelial cells in culture. Platelet-poor plasma from uraemic patients causes an increased rate of synthesis and release of prostacyclin in the same system.19 The precise nature of this factor, which is present in normal and uraemic plasma, has not been determined. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation and the findings of this study could thus explain the defective platelet-endothelial interaction and consequent prolonged bleeding time of uraemic patients. A decreasing effect of treatment modalities known to improve the uraemic bleeding diathesis, e.g. haemodialysis, on prostacyclin production by vascular endothelial cells in vivo could help to substantiate this.

The clinical application of these results is still uncertain. Selective pharmacological inhibition of vascular endothelial cell cyclo-oxygenase or prostacyclin synthetase would be the theoretical solution to the problem, but such an agent is not yet available. It has been shown in in vitro experiments that vitamin Kc can inhibit prostacyclin production by bovine vascular endothelial cells.20 As far as could be ascertained, this substance has not been clinically used for the treatment of the uraemic bleeding tendency. This widely available and inexpensive form of treatment, that could correct one of the basic pathophysiological defects of haemostasis in the uraemic patient, should be evaluated in a clinical trial.

The author wishes to thank the Renal Unit, Tygerberg Hospital, for permission to study their notes and also Mrs E. Fourie and Mrs H. Cloete for expert technical assistance.

REFERENCES

Anaesthesia without tears

M. SCHREUDER, A. T. BOSENBERG, W. B. MURRAY

Rectal induction of anaesthesia is a useful method but is not widely used in South Africa. We studied the onset of action and side-effects of 1% methohexitone administered rectally in a dose of 20 mg/kg to 110 preschool children. Ninety-one per cent were adequately sedated for inhalation induction by mask within 10 minutes, and all by 15 minutes, of drug administration. There was no evidence of significant cardiovascular or respiratory depression and only minor complications such as faecal soiling (11.8%) and hiccup (3.6%) were noted.

The technique has been favourably received by parents, surgeons and nursing staff and has now become routine practice.

Methods

Preschool children, ASA physical status I and II, presenting for elective surgery during a 6-month period were studied prospectively. Both outpatients and inpatients were involved. Children under the age of 6 months or those in whom a 'difficult airway' was suspected were excluded from the study.

During the routine pre-operative visit the procedure was explained to both parent and child and the age, sex and weight were noted. No additional pharmacological premedicant was prescribed.

At the time of surgery the child was accompanied to the operating room by a parent or caring adult. In the operating room the child was placed in the lateral position while the parent talked to and comforted the child as required.

A freshly prepared 1% methohexitone solution in a dose of 20 mg/kg to a maximum of 500 mg was injected rectally via a soft red rubber catheter (Jacques) using a 10 ml or 20 ml plastic syringe. The catheter was lubricated with KY jelly and was inserted to a depth of 2 cm. The time of injection was noted. Following the injection, the buttocks were taped together in an attempt to prevent any loss of medication.

At 10 and 15 minutes after the injection the level of consciousness of the child was assessed. 'Asleep' was defined as no response to the application of a face-mask, 'sedated' as response to the mask or the introduction of halothane, and 'awake' as resistance to the face-mask.