CLINICAL RESEARCH

Prostacyclin and thromboxane A₂ in thrombotic thrombocytopenic purpura

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Abstract

A study was conducted to find whether a deficiency in prostacyclin (prostaglandin I₂; PGI₂) is implicated in the pathogenesis of thrombotic thrombocytopenic purpura. Plasma samples from two patients with the disease before treatment and from 22 healthy controls were therefore assayed for concentrations of 6-oxo-PGF_{1α} and thromboxane B₂, the stable metabolites of PGI₂ and thromboxane A₂, respectively. Neither of the patients responded to treatment, which in one case included an infusion of PGI₂.

Both patients had normal concentrations of 6-oxo-PGF_{1α} and thromboxane B₂, thus implying that circulating amounts of PGI₂ and thromboxane A₂ were also normal.

These findings suggest that 6-oxo-PGF_{1α} may be detectable in normal amounts in thrombotic thrombocytopenic purpura and that the condition need not be associated with a high concentration of thromboxane A₂.

Introduction

Thrombotic thrombocytopenic purpura is a rare fulminating disorder characterised by microangiopathic haemolytic anaemia, thrombocytopenia, neurological and renal abnormalities, and fever. Deficiency of the platelet antiaggregatory agent prostacyclin (prostaglandin I₂; PGI₂) might explain the platelet

consumption and widespread disseminated intravascular thromboses observed in the condition. Two patients with thrombotic thrombocytopenic purpura have been described in whom 6-oxo-PGF_{1α}, the stable metabolite of PGI₂, was undetectable.^{1,2} In one case an infusion of PGI₂ produced no improvement, but it was suggested that this might have been due to high circulating concentrations of the proaggregatory agent thromboxane A₂.¹ Other studies, however, contain no information on the concentration of thromboxane B₂, the stable metabolite of thromboxane A₂, in thrombotic thrombocytopenic purpura. Recently a case was reported showing accelerated plasma degradation of exogenous PGI₂. The pretreatment concentration of 6-oxo-PGF_{1α} was not given, though when the patient's plasma was incubated with aortic rings it generated normal 6-oxo-PGF_{1α} values.³

We describe two patients with thrombotic thrombocytopenic purpura, one of whom received an infusion of PGI₂, and report the pretreatment concentrations of 6-oxo-PGF_{1α} and thromboxane B₂ in these cases and in a control group of healthy volunteers.

Case reports

Case 1—A previously fit 23-year-old woman was admitted to hospital with a two-day history of nausea, headache, myalgia, and transient loss of consciousness. Examination showed a temperature of 37.5°C, petechiae on arms and legs, pallor, jaundice, and hepatomegaly. Haemoglobin concentration was 7.7 g/dl, white cell count $5.9 \times 10^9/l$ ($5900/mm^3$), and platelets $17 \times 10^9/l$ ($17\,000/mm^3$), and the blood film showed pronounced red-cell fragmentation. Urine analysis showed heavy proteinuria and haematuria. She failed to respond to fresh-frozen plasma, prednisolone 80 mg/day, and plasmapheresis and was also given synthetic PGI₂ (Wellcome Pharmaceuticals) intravenously at a dose of 10 ng/kg/min over 12 hours with no clinical or haematological improvement. During the next five days she had two episodes of hemianaesthesia followed by headache, bradycardia, and vomiting and became comatose. She died nine days after admission. Necropsy showed that the immediate cause of death was cerebellar tonsillar herniation. Petechial haemorrhages and microscopic hyaline thrombi in the arterioles and capillaries were found in the brain, heart, liver, kidneys, adrenals, pancreas, and spleen.

Case 2—A 60-year-old man was admitted to hospital after transient loss of consciousness. He also had a two-day history of passing dark

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urine. Subsequently he became confused and disorientated. On examination his temperature was found to be 37.8°C and he was jaundiced and drowsy, with petechiae on arms, legs, and trunk. Haemoglobin concentration was 9.0 g/dl, white cell count $5.0 \times 10^9/l$, and platelets $< 10 \times 10^9/l$, and the blood film showed pronounced red-cell fragmentation. Urine analysis showed heavy proteinuria and haematuria. He was treated with fresh-frozen plasma, hydrocortisone 200 mg six-hourly intravenously, heparin 1000 IU/h, and intravenous dipyridamole 100 mg with no clinical or haematological improvement. He became comatose shortly after arrival and died two days after admission. Permission for necropsy was refused.

Methods and results

Plasma samples were collected from the two patients before treatment and from 22 healthy male and female laboratory staff and stored at -30°C until assayed. Samples were buffered to pH 4.0 and prostaglandins extracted with ethyl acetate. Extracts were measured by radioimmunoassay for 6-oxo-PGF_{1α}⁴ and thromboxane B₂. The method for thromboxane B₂⁵ was modified, antibody-bound thromboxane B₂ being extracted by using donkey antirabbit IgG precipitating serum (Scottish Antibody Production Unit). The mean recovery from the extraction procedure, established with ³H-6-oxo-PGF_{1α} and ³H-thromboxane B₂ (New England Nuclear) as tracers, was $95 \pm \text{SD } 3\%$ and $94 \pm 1\%$ ($n=5$) for 6-oxo-PGF_{1α} and thromboxane B₂, respectively. Interassay and intra-assay coefficients of variation were $2.0 \pm 0.1\%$ and $3.1 \pm 0.2\%$, respectively, for 6-oxo-PGF_{1α}, and 10.7% and 12.1%, respectively, for thromboxane B₂. The table shows the values recorded.

Comment

Occasional remissions have been reported in thrombotic thrombocytopenic purpura with various forms of treatment,⁶ but our two patients failed to respond to several forms of treatment, including an infusion of PGI₂ in case 1. The plasma concentrations of 6-oxo-PGF_{1α} and thromboxane B₂ were

Plasma concentrations of 6-oxo-PGF_{1α} and thromboxane B₂ in cases 1 and 2 and 22 healthy subjects

	Case 1	Case 2	Healthy subjects	
			Range	Mean $\pm$ SD
6-oxo-PGF _{1α} (μg/l)	0.83	0.80	0.16–0.83	0.50 $\pm$ 0.17
Thromboxane B ₂ (μg/l)	5.90	4.10	0.15–13.80	2.62*

*Geometric mean of skewed distribution.

normal in both patients, implying that amounts of the circulating precursor compounds PGI₂ and thromboxane A₂ were also normal. In these two patients we therefore did not find the deficiency of PGI₂ that has been suggested as a factor in the pathogenesis of thrombotic thrombocytopenic purpura, though we cannot comment on the rate of PGI₂ degradation. We conclude that 6-oxo-PGF_{1α} is detectable and may be in normal concentration in thrombotic thrombocytopenic purpura and that this condition need not be associated with a high concentration of thromboxane A₂.

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(Accepted 22 September 1981)

A relation between high-density-lipoprotein cholesterol and bile cholesterol saturation

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Abstract

The association of cholesterol gall stones with coronary artery disease is controversial. To investigate this possible relation at the biochemical level, bile cholesterol saturation and the plasma concentrations of triglycerides, total cholesterol, and high-density-lipoprotein cholesterol (HDL cholesterol) were measured in 25 healthy, middle-aged women. Bile cholesterol saturation index was negatively correlated with HDL cholesterol. It was positively correlated with plasma triglycerides and with total cholesterol minus HDL cholesterol.

These findings provide a biochemical basis for a positive association in women between cholesterol gall stones and coronary artery disease.

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Introduction

The association of cholesterol gall stones with coronary artery disease is controversial. Some early necropsy studies showed an increased prevalence of gall stones in patients with severe coronary artery disease¹ and in patients who had died of myocardial infarction,^{2,3} whereas another study did not find any definite relation.⁴ Later epidemiological studies were also conflicting, showing, in women, both positive⁵ and negative⁶ associations.

A way to investigate the association may be to look for correlations between plasma and biliary lipid concentrations. Conceivably, a low concentration of high-density-lipoprotein cholesterol (HDL cholesterol) might underlie and explain a positive association between ischaemic heart disease and cholesterol gall stones. Cholesterol is kept in solution in bile by the action of bile acids and phospholipids. If the cholesterol excreted into bile exceeds this solubilising capacity, bile becomes supersaturated with cholesterol and apt to precipitate gall stones.⁷ HDL cholesterol is an important protective factor against coronary artery disease.⁸⁻¹¹ The cholesterol taken up by high-density lipoprotein is believed to be excreted in bile.^{12,13}