PAPERS AND SHORT REPORTS

Central venous concentrations of immunoreactive prostaglandins E, F, and 6-keto-prostaglandin F₁ in eclampsia

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Abstract

Concentrations of prostaglandins E, F, and 6-keto-prostaglandin F₁ were estimated in central venous blood and amniotic fluid in 21 women with eclampsia and 16 healthy pregnant controls. Central venous blood concentrations of 6-keto-prostaglandin F₁ and prostaglandin E were significantly lower in patients than controls before delivery and remained reduced for at least 48 hours after delivery.

Low concentrations of prostaglandins E and 6-keto-prostaglandin F₁ are probably directly related to the pathogenesis of eclampsia.

Introduction

Recent evidence of a deficiency of prostacyclin, a vasodilatory prostaglandin, in umbilical arteries,¹ uterine tissue,² and amniotic fluid³ in patients with pre-eclampsia has renewed interest in the aetiology of this condition. Despite these reports there has not been unanimity about decreased concentrations of 6-keto-prostaglandin F₁, a metabolite of prostacyclin, in maternal peripheral venous blood. Indeed, Koullapis *et al* found higher concentrations of 6-keto-prostaglandin F₁ and thromboxane B₂ in women who developed pre-eclampsia than normotensive pregnant women.⁴ Data from studies on intra-uterine tissues have also not been conclusive.^{5,6}

Such inconsistent results may be due to prostaglandins being labile substances that are rapidly metabolised by the lungs and

are therefore difficult to measure. In addition, there is disagreement about the absolute values for concentrations of prostanoid metabolites in peripheral venous blood during pregnancy; women included in many of the studies have not been homogeneous. To obviate these problems we estimated the concentrations of prostaglandins E, F, and 6-keto-prostaglandin F₁ in central venous blood in 21 women with eclampsia and 16 healthy controls.

Subjects and methods

SUBJECTS

We studied 21 women (mean (SD) age 19 (4.4) years) who presented with hypertensive crises in pregnancy. Eighteen presented with convulsions associated with hypertension and proteinuria; were semiconscious, and were judged clinically to have viable pregnancies; neither the relatives of these patients nor the patients at discharge from hospital gave any history of epilepsy. The three other patients studied had imminent eclampsia—that is, severe proteinuric hypertension with epigastric pain, blurring of vision, photophobia, nausea and vomiting, or persistent headache, or a combination of these. On admission all 21 patients had diastolic blood pressures greater than 110 mm Hg, and all had ++ proteinuria as measured with dipsticks on at least two occasions.

Patients were managed by standard procedures. Prophylaxis against convulsions was with magnesium sulphate, 4 g intravenously and 5 g intramuscularly in each buttock as a loading dose on admission and then 5 g intramuscularly every four hours for 24 hours; and diazepam 10 mg was given on admission to control restlessness and irritability. Blood pressure was lowered, if necessary, with dihydralazine 6.25 mg intravenously. A central venous line with a "drum" catheter (Abbott) was inserted through a peripheral vein in the antecubital fossa for measurement of central venous pressure. The position of the catheter tip was checked by x ray examination and the catheter left in place for about 48 hours. Acidosis, if present as shown by blood gas analysis of a heparinised sample of blood from the radial artery, was corrected by infusing the appropriate amount of sodium bicarbonate and monitoring urinary output. There was early recourse to caesarean section under general anaesthesia if vaginal delivery was judged unlikely to occur within six hours after admission. All 21 women with eclampsia were delivered by lower segment caesarean section.

We also studied a group of 16 women (mean (SD) age 21 (3.2)

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years) undergoing elective caesarean section because of obstetric complications. None of the women in this group had any medical complication; they were either primigravidas or in their second pregnancies. The mean parity in this group was 1 (0.9). All 16 controls had consented to participate in the study after being informed of its purpose. They did not receive magnesium sulphate or antihypertensive agents, but a central venous line with a drum catheter was used as an intravenous channel during anaesthesia and recovery from the operation.

SAMPLING METHODS

Maternal serum—Samples of central venous blood were obtained before anaesthesia, at the time of delivery, and on the first and second days after caesarean section. Free flow of blood obtained from the central venous line was collected in tubes containing aspirin, which were immediately conveyed on ice to be centrifuged, and the plasma was stored at -20°C . Assays were done within two weeks of collection.

Amniotic fluid—Samples of amniotic fluid were obtained in 15 women (five with eclampsia and 10 controls) by amniocentesis under direct vision just before the uterus was incised at caesarean section.

MEASUREMENT OF PROSTAGLANDINS

Specific radioimmunoassay of prostaglandins E, F, and 6-keto-prostaglandin $\text{F}_{1\alpha}$ was done according to methods previously described.^{7,8} Antibodies were raised in rabbits against bovine serum albumin conjugates of the relevant compound; the cross reactions of the antibodies have been described elsewhere.⁸ Samples of serum and amniotic fluid, to which a known quantity of the appropriate tritiated ligand had been added, were extracted with ethyl acetate; the solvent was evaporated to dryness. Serum samples were submitted to silicic acid chromatography and the appropriate fractions collected. The final fraction was dried and reconstituted with phosphate buffer (pH 7.4); measured portions were taken to measure the extraction recovery and to measure the prostanooids by radioimmunoassay. Samples yielding extraction recovery of less than 70% were excluded from the final analysis. Separation of bound and free prostanooids was done with charcoal coated with dextran and the supernatant counted in a liquid scintillation spectrometer.

STATISTICAL ANALYSIS

The data obtained were not normally distributed. The Mann-Whitney U test and Friedman two way analysis of variance were consequently used to test significance. We chose 5% as the level of significance.

Results

One woman with eclampsia gave birth to a growth retarded infant that weighed 1400 g and died of birth asphyxia two days after delivery. There were no other perinatal deaths.

Serum prostaglandin concentrations—On admission to hospital concentrations of immunoreactive prostaglandin E and 6-keto-prostaglandin $\text{F}_{1\alpha}$ were significantly reduced ($p < 0.001$) in 21 and 18 patients with eclampsia respectively when compared with the controls (figure and table), but concentrations of prostaglandin F did not differ.

Comparison of concentrations of prostaglandin E and 6-keto-prostaglandin $\text{F}_{1\alpha}$ in patients and controls. (Samples yielding extraction recovery of less than 70% have not been included.)
Conversion: SI to traditional units—Prostaglandin E: 1 nmol/l $\approx$ 35.3 ng/100 ml. 6-Keto-prostaglandin $\text{F}_{1\alpha}$: 1 nmol/l $\approx$ 37.1 ng/100 ml.

Median (range) prostaglandin concentrations (nmol/l) in central venous blood from 21 pregnant women with eclampsia and 16 pregnant controls

	Before delivery		At delivery		Day 1		Day 2	
	Controls	Patients	Controls	Patients	Controls	Patients	Controls	Patients
Prostaglandin E	2.26 (1.29-3.39)	1.22 (0.74-3.33) $p < 0.0001$	2.50 (0.94-2.64)	1.42 (0.86-5.32) $p < 0.001$	2.24 (1.04-4.40)	1.18 (0.31-2.36) $p < 0.0005$	2.40 (0.87-3.82)	1.22 (0.50-2.90) $p < 0.0005$
6-keto-prostaglandin $\text{F}_{1\alpha}$	2.25 (1.74-2.74)	0.98 (0.54-1.85) $p < 0.0001$	2.23 (1.54-3.81)	1.07 (0.43-1.97) $p < 0.001$	2.03 (1.30-3.84)	1.04 (0.38-1.80) $p < 0.0005$	2.11 (0.16-2.71)	1.00 (0.60-2.16) $p < 0.0005$
Prostaglandin F	6.50 (2.99-16.79)	7.22 (1.73-17.47)	4.46 (2.89-11.98)	6.36 (1.49-16.75)	4.86 (2.19-20.60)	4.66 (0.65-14.34)	4.20 (1.37-8.27)	5.27 (1.41-15.71)

Conversion: SI to traditional units—Prostaglandin E: 1 nmol/l $\approx$ 35.3 ng/100 ml. 6-Keto-prostaglandin $\text{F}_{1\alpha}$: 1 nmol $\approx$ 37.1 ng/100 ml. Prostaglandin F: 1 nmol $\approx$ 48.1 ng/100 ml.

These significant differences in concentrations of prostaglandin E and 6-keto-prostaglandin $F_{1\alpha}$ were also found at the time of operation ($p < 0.001$) and at 24 and 48 hours after delivery ($p < 0.0005$). Analysis of the variance within the groups of women with and without eclampsia by the Friedman procedure indicated that there was no significant change within the two groups in any of the prostaglandins during the time of the study.

Prostaglandin concentrations in amniotic fluid—Median concentrations (and ranges) of prostaglandins E, F, and 6-keto-prostaglandin $F_{1\alpha}$ in amniotic fluid were 1.64 (1.12-3.07) nmol/l (57.9 (39.5-108.4 ng/100 ml), 0.55 (0.44-0.75) nmol/l (26.5 (21.2-36.1) ng/100 ml), and 0.51 (0.25-1.25) nmol/l (18.9 (9.3-46.4) ng/100 ml) respectively in patients and 2.90 (1.41-4.33) nmol/l (102.4 (49.8-152.8) ng/100 ml), 0.81 (0.38-1.81) nmol/l (40.8 (18.3-87.1) ng/100 ml), and 0.41 (0.12-0.92) nmol/l (15.5 (4.5-34.5) ng/100 ml) in controls. Thus there were no significant differences in amniotic fluid concentrations between patients and controls.

Discussion

Controversy about the definition of pre-eclampsia and its severity has complicated previous studies on the role of prostaglandins in the pathophysiology of this condition. We sought to obviate these problems by investigating patients who had developed eclampsia as evidenced by severe proteinuric hypertension with convulsions. They were therefore relatively homogeneous in respect of the severity of the condition.

Other studies have, of necessity, measured peripheral venous concentrations of prostaglandins with the inherent problems of metabolism of some primary prostaglandins after circulation through the lungs. In the present investigation these compounds were measured in central venous blood before passage through the lungs. Although the concentrations were considerably higher than those measured by mass spectrometry,⁹ those in the controls were within limits normally obtained by radioimmunoassay in pregnancy. The significantly decreased plasma concentrations of prostaglandins E and 6-keto-prostaglandin $F_{1\alpha}$ are therefore of great importance (table). Although an effect of the drug treatment cannot be excluded, we are not aware of any effect of magnesium sulphate on production of prostaglandins; the low concentrations seen before treatment was started and the unchanged concentrations 24 hours after magnesium was stopped militate against a drug induced effect. Thus the low concentrations of vasodilatory prostaglandins were probably directly related to the pathogenesis of eclampsia. By contrast, the concentrations of all prostaglandins in amniotic fluid were not significantly different between the patients and controls. This accords with our previous observations that concentrations of 6-keto-prostaglandin $F_{1\alpha}$ and thromboxane B_2 are not altered in amniotic fluid obtained from pregnant women before the onset of eclampsia and supports the contention that abnormalities in production of prostanoids in pre-eclampsia are reflected in vascular tissue rather than in the membranes and deciduums.¹⁰

Gant *et al* proposed that the relative vascular refractoriness to angiotensin II that characterises normal pregnancy results from the action of a prostaglandin or prostaglandin related substance on vascular smooth muscle.¹¹ In pre-eclampsia a deficiency of the prostaglandin may increase sensitivity and play a part in enhanced vascular sensitivity to circulating vasoconstrictor substances. Prostaglandin E and prostacyclin could theoretically satisfy the criteria for this vasodepressor prostanoid, although Barrow *et al* suggested that the concentrations of prostaglandin I_2 in maternal plasma are too low for it to act as a circulating hormone in normal pregnancy.⁹ This does not exclude a local

effect in the uterine and placental vessels, however, and several studies have shown that maternal and fetal vessels produce less prostaglandin I_2 in pre-eclampsia.¹² The present study showed an appreciable reduction in concentrations of prostaglandins and keto-prostaglandin $F_{1\alpha}$ in patients with eclampsia, which persisted for at least 48 hours after delivery. This suggests that, although the uteroplacental vessels may be the major source of increased production of prostacyclin in pregnancy, a more generalised deficiency of vasodilatory prostaglandins may be present in severe pre-eclampsia and eclampsia. It also raises the possibility that infusion of prostacyclin may be important in treating the life threatening condition eclampsia.

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Correction

Glycaemic control in diabetic nephropathy

We regret that errors occurred in this paper by Dr J J Bending and others (21 April, 1187-91). In the final paragraph, line 9 should have read "... care in diabetic patients who have lost both hormonal counterregulation and warning symptoms of hypoglycaemia" and line 17 should have read "... must be balanced against the risks of hypoglycaemia." In the legend to figure 1 two symbols became transposed. The legend should have read "Mean (SD) circadian plasma glucose concentrations in diabetics with proteinuria receiving conventional insulin injection (○—○), diabetics without proteinuria receiving continuous subcutaneous insulin infusion (□---□), and diabetics with proteinuria and receiving continuous subcutaneous insulin infusion (●—●).".