Cardiovascular collapse following an overdose of prostaglandin F_2 alpha: a case report

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A case report is presented of a parturient who suffered severe hypotension and pulmonary oedema following an overdose of intramyometrial prostaglandin F_2 alpha. Oxytocin induction of labour in this patient led to a rapid delivery, followed by a hypotonic uterus and postpartum haemorrhage. After resuscitation with blood and crystalloid fluids, the uterus was explored under general anaesthesia. The uterus was free of retained products but the lower uterine segment failed to contract despite bimanual uterine compression and intravenous oxytocin. Prostaglandin F_2 alpha was injected into the lower uterine segment via a transvaginal approach. This was rapidly followed by cardiovascular collapse and later by pulmonary oedema. The differential diagnosis and subsequent management are discussed.

Key words
ANAESTHESIA: obstetrical; COMPLICATIONS: bleeding, hypotension; HAEMORRHAGE: postpartum; HORMONES: prostaglandins; prostaglandin F_2 alpha; LUNG: oedema.

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The effectiveness of prostaglandin F_2 alpha and its 15-methyl analogue to induce abortion and labour has led to their increasing use. Intramyometrial injection of these compounds has been advocated to control postpartum haemorrhage secondary to placenta accreta and uterine hypotonia.[1,2,3] Their reported side effects include nausea, vomiting, diarrhoea as well as pulmonary and systemic hypertension[4] and severe bronchospasm.[5] The following is a case report of intramyometrial injection of an excessive dose of prostaglandin F_2 alpha resulting in profound hypotension and pulmonary oedema.

Case report

A 31-year-old North American native woman was admitted at 35 weeks gestation because of pregnancy-induced hypertension and vaginal bleeding. Her past history included the birth of a term infant 14 years before and a therapeutic abortion. There was no history of allergy or of preexisting cardiovascular disease. The pertinent admission findings included: blood pressure 160/100 mmHg, marked oedema of the lower extremities, 4 + proteinuria, haemoglobin 113 $g \cdot L^{-1}$ and a normal coagulogram. Ultrasound examination revealed a low-lying placenta. Induction of labour was commenced with IV oxytocin. After a 3 hour 25 minute first stage, the patient had a one minute second stage, with delivery of a healthy, male child. The placenta delivered spontaneously six minutes later. Minimal bleeding had continued throughout labour, but following delivery, brisk bleeding ensued; the loss was estimated at 3000 ml. The patient's blood pressure decreased to 85 mmHg systolic with a heart rate of 165 bpm. Resuscitation followed. Additional IV lines were inserted, IV oxytocin was administered and bimanual uterine compression was performed. Two units of matched packed red blood cells and two litres of saline were administered. Her BP stabilized at 120/75 and her HR decreased to 115 bpm.

As there was continuing blood loss in spite of these measures, it was decided to examine her under general anaesthesia. Forty minutes after delivery and following

preoxygenation and cricoid pressure, anaesthesia was induced with thiopentone 150 mg and succinylcholine 100 mg and the trachea was intubated. Chest auscultation revealed bilateral, clear air entry. Anaesthesia was maintained with nitrous oxide (50 per cent) and oxygen and IV fentanyl (total 200μg) in incremental doses. During the procedure the patient's blood pressure increased to 150/90 with a sinus tachycardia of 115–120 bpm. Following manual exploration and curettage, which failed to reveal retained products, there was continuing blood loss, considered to be secondary to a poorly contractile lower uterine segment. A vial of prostaglandin F_2 alpha (40 mg) was diluted in 30 ml saline and the entire amount was injected incrementally into the lower uterine segment. The anaesthetist was unaware of the amount of prostaglandin F_2 alpha injected. Examination of the patient immediately following injection revealed a blood pressure of 150/90 and normal breath sounds. Three to four minutes later the bleeding had stopped and prior to removing the patient from the lithotomy position an attempt was made to recheck the blood pressure. At this time there was no palpable pulse and the blood pressure was unobtainable. The ECG still showed a sinus tachycardia of 130. Ventilation of the lungs with 100 per cent oxygen and rapid infusion of saline and packed red cells was given in an attempt to restore the blood pressure. Incremental administration of IV ephedrine (total 50 mg), epinephrine (total 1 mg) and phenylephrine (total 4 mg) over a period of 20 minutes failed to improve the situation. The femoral pulse would fleetingly return and then disappear. The patient's extremities were warm and appeared vasodilated. Solucortef 300 mg was administered. Following development of ventricular premature beats, a bolus of lidocaine (60 mg) was given. An internal jugular central venous pressure line was established for drug administration. However, minutes later, fulminant pulmonary oedema developed with copious amounts of frothy, pink sputum coming from the tracheal tube. A dopamine infusion was initiated through the central venous line and the patient developed a palpable femoral pulse and a systolic blood pressure of 80 mmHg. Blood was drawn for arterial blood gas analysis which showed a pH of 7.12, PaO_2 of 150 torr, $PaCO_2$ of 48 mmHg. The patient stabilized with a systolic blood pressure of 90 mmHg, and was transferred, conscious, to the intensive care unit (ICU). In the ICU, a Swan Ganz catheter was inserted and the initial pulmonary capillary wedge pressure was 25 cm H_2O. Due to technical difficulties further readings were not obtained until three hours later at which time the PCWP was 6 cm H_2O, pulmonary artery pressure was 20/8 mmHg and the right atrial pressure was 3 cm H_2O. Her systemic blood pressure at that time was 130/80 mmHg. Ventilation was controlled on 100 per cent oxygen and she received furosemide to promote diuresis. A repeat coagulogram in the ICU was normal. Over the next few hours her condition steadily improved and her trachea was extubated 17 hours postpartum. Total fluids received during the resuscitation were eight litres saline and six units packed red blood cells. She was discharged from hospital four days postpartum with a haemoglobin of 105 $g \cdot L^{-1}$.

Follow-up investigations included an echocardiogram and examination of the transfused blood to ensure that it was pathogen- and leukoagglutinin-free. These tests were normal. Allergy testing to the anaesthetic agents was also done and was negative. A subsequent general anaesthetic was uneventful.

Discussion

A major difficulty was to determine the cause of cardiovascular collapse as the anaesthetist was unaware that an overdose of PGF_2 alpha had been given.

The differential diagnosis for the cause of sudden collapse in our patient included: a reaction to the PGF_2 alpha, an anaphylactic reaction to the anaesthetic agents used, or transfusion-related acute lung injury (TRALI, pulmonary leukoagglutinin reaction). Amniotic fluid embolus, another cause of cardiovascular decompensation, was unlikely in this patient as collapse followed delivery by approximately 60 minutes.

Prostaglandins are naturally occurring substances and prostaglandin F_2 alpha (PGF_2 alpha) has been shown to induce uterine contractions in the term uterus. Takagi *et al.*[2] demonstrated that direct intramyometrial injection of PGF_2 alpha was effective in causing uterine contraction in cases of severe postpartum haemorrhage which were unresponsive to oxytocin, ergonovin and uterine massage. The minimum effective dose was 250 μg but 1.0 mg was routinely used. Bruce *et al.*[6] reported on the use of 15-methyl PGF_2 alpha (a more potent analogue of PGF_2 alpha) in five cases of uterine atony with severe blood loss and found that three of the five patients responded well, and hysterectomy was avoided. In all three patients oxytocin, ergometrine and uterine massage had proven ineffective. Hayashi *et al.*[7] suggested that it is less effective if chorioamnionitis is present.

Side effects of PGF_2 alpha are usually related to its potent effects on smooth muscle. Secher *et al.*[8] found that during infusion of 300 μg of PGF_2 alpha in pregnant, anaesthetized women there was a 40 per cent increase in cardiac output and a 25 per cent increase in femoral arterial pressure. They demonstrated an increase in pulmonary arterial pressure, doubling of pulmonary vascular resistance and an 11 per cent decrease in systemic resistance. As well, airway resistance increased. Weir *et al.*[5] demonstrated bronchoconstriction with IM injection

of PGF_2 alpha in healthy women, without respiratory symptoms. They recommended it not be used in patients with a history of asthma.

Hayashi *et al.*[7] reported infrequent and mild side effects in a clinical study of 51 patients. These included nausea, vomiting and diarrhoea. Diastolic blood pressure changes were variable (32 increased, 16 decreased and six were unchanged). Mayhew[9] reported a case of hypertension following intramyometrial prostaglandin F_2 alpha in an anaesthetized patient. The hypertension gradually subsided over a few minutes. Sudden collapse and death have been reported by Cates[10] following the use of PGF_2 alpha, intraamniotically for abortion. In one of these patients, severe hypertension developed. Other PGF_2 alpha-related deaths have been reported[11] but these did not appear to bear a direct relationship to its use.

A recent paper by Hankins *et al.*[12] reported on the development of marked maternal arterial oxygen desaturation within five to ten minutes of administration of the 15-methyl analogue of PGF_2 alpha, secondary to acute increases in the intrapulmonary shunt. Their five patients required ventilatory support for from one to eighteen hours.

The temporal sequence in this particular case supports PGF_2 alpha as the cause of the cardiovascular collapse. The recommended dose for intramyometrial injection is 1–5 mg.[2] This patient received 40 mg. Secher[8] demonstrated that IV infusion of PGF_2 alpha resulted in a doubling of pulmonary vascular resistance and a decrease of 11 per cent in systemic resistance, which would fit with this clinical picture. There was significant delay in our patient in the development of pulmonary oedema. The combination of acute pulmonary hypertension with decreased left ventricular end diastolic pressure and decreased cardiac output, as well as relative fluid overload, may have ultimately resulted in left heart failure. Although systemic hypertension[4,9] has been reported in association with PGF_2 alpha use, it is important to realize that hypotension may also occur.

Allergic reactions associated with anaesthetic agents are uncommon, but appear to be increasing.[13] Anaphylactic and anaphylactoid reactions have been reported after thiopentone and succinylcholine. Clinically, in addition to hypotension and tachycardia, bronchospasm and urticaria are seen frequently.

The other diagnostic possibility is a reaction to the blood transfusion. This could have been due to infusion of infected blood or a reaction to leukoagglutinins in the donor blood. Transfusion-related acute lung injury (TRALI) is infrequent but potentially life-threatening.[14,15] Typically, it presents as acute respiratory distress characterized by hypoxaemia and fulminant pulmonary oedema. Symptoms usually develop within four hours of transfusion and are accompanied by hypotension. In most cases granulocyte or lymphocyte antibodies are found in the serum of the implicated plasma containing blood products. While the clinical picture of hypotension and fulminant pulmonary oedema is consistent with this diagnosis, the absence of antibodies would tend to rule it out.

This case report underlines several important points. Whenever a new drug, or an old drug with a new use, becomes available, it is important that all staff become familiar with the appropriate dose for each indication. Prostaglandin F_2 alpha has been available in a 40 mg ampoule for intraamniotic injection to induce abortion. It is only recently that its use for severe postpartum haemorrhage, secondary to a hypotonic or atonic uterus, has been recognized. Since it has potent effects on smooth muscle, care must be taken to ensure that it is not injected intravascularly and that the correct dose is used.

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Résumé

Il se peut qu'un surdosage de prostaglandine F_2 alpha injectée dans le myomètre entraine de l'hypotension et de l'oedème pulmonaire; en voici un exemple. Avec stimulation aux ocytociques, une patiente accouche rapidement mais l'utérus devient atone et saigne abondamment. On infuse alors du sang et des solutions de cristalloïdes, suivis d'un curetage sous anesthésie générale qui confirme l'absence de rétention placentaire. Le segment inférieur de l'utérus demeure flasque malgré le massage utérin et l'ocytocine intraveineuse. C'est alors que par voie vaginale, l'on injecte de la prostaglandine F_2 alpha dans l'utérus. Il s'ensuit rapidement un collapsus cardiovasculaire et un oedème pulmonaire. Voir l'article pour le diagnostic différentiel et la suite des événements.