Pulmonary oedema after hexoprenaline administration in preterm labour

A report of 4 cases

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Summary

Despite the widespread use of β-sympathomimetic agents for preterm labour there appears to be a limited appreciation of the need for cardiovascular monitoring in the mother. Four patients in whom pulmonary oedema developed during tocolysis with hexoprenaline are described and the aetiological factors and pathogenesis of this potentially lethal complication discussed. Guidelines for the safe use of hexoprenaline in preterm labour are suggested.

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Complications associated with the use of β-sympathomimetic agents in preterm labour have been reviewed by Benedetti.[1] Pulmonary oedema, myocardial ischaemia, cardiac arrhythmia, cerebral vasospasm, hypotension, hyperglycaemia and hypokalaemia have all been reported.

Pulmonary oedema is an adverse reaction unique to the parturient patient and has been reported with most of the commonly used tocolytic agents, including ritodrine,[2] terbutaline[3] and salbutamol.[4] No cases of pulmonary oedema associated with the use of hexoprenaline in preterm labour have, to our knowledge, been reported.

We report 4 cases of pulmonary oedema in patients who received hexoprenaline with or without corticosteroids and/or indomethacin for preterm labour.

Case reports

Case 1

A 25-year-old primigravid woman with a previously uncomplicated twin pregnancy was admitted to hospital in labour at 32 weeks' gestation.

The patient had no previous history of cardiovascular disease or serious illness. The arterial blood pressure was 120/80 mmHg on admission and the heart rate 72/min. Auscultation of lungs and heart revealed no abnormality and the jugular venous pressure was not elevated. The cervix was 3 cm dilated, well effaced and the membranes were intact. The presenting part of the leading twin was cephalic, at the level of the ischial spines. The fetal heart rates were normal. Contractions were fairly strong and 3 - 4 minutes apart. The haemoglobin level was 13,3 g/dl and the leucocyte count 13,8 × 10^9/l. There was no clinical evidence of chorio-amnionitis.

An infusion of hexoprenaline was started. A dose of 1,20 μg/min was required to suppress uterine action. The pulse rate varied between 95 and 120/min. Betamethasone 12 mg was administered to accelerate fetal lung maturity and repeated 12 hours later. After 72 hours of treatment the patient complained of tightness of the chest and shortness of breath. On examination she was tachypnoeic with a respiratory rate of 24/min, centrally cyanosed, coughing and pyrexial (37,8°C). The blood pressure was 160/100 mmHg and the pulse rate 130/min and regular. Early inspiratory crepitations could be heard at both lung bases. Arterial partial pressure of oxygen (PaO_2) was 45,8 mmHg, arterial carbon dioxide tension ($PaCO_2$) 20,8 mmHg and the pH 7,47. Chest radiography showed features of pulmonary oedema. The ECG was normal, apart from a sinus tachycardia. A positive fluid balance of 3 700 ml was recorded over the 72-hour period.

Oxygen was administered (4 l/min by face mask). The hexoprenaline infusion was discontinued and furosemide 40 mg was given intravenously. The PaO_2 improved only slightly to 54,5 mmHg despite the supplementary oxygen administration.

Artificial rupture of the membranes was performed and 2 hours later the first twin was delivered with Anderson's forceps. The second infant was delivered by assisted breech delivery with forceps to the aftercoming head. The first infant weighed 1 800 g and had Apgar scores of 9 and 10. The second infant weighed 1 280 g and the Apgar scores were 7 and 9.

Immediately after delivery the patient was transferred to the intensive care unit where endotracheal intubation and assisted ventilation were commenced.

After 6 hours, ventilatory and gas exchange function improved and the patient was weaned to spontaneous ventilation with constant positive airway pressure. She was successfully extubated on the 3rd post-partum day and discharged well on the 10th post-partum day.

Cases 2, 3 and 4

To avoid repetition, the salient features of all 4 cases are listed in Table I. The ages of the patients varied from 20 years to 36 years and the period of gestation was between 28 and 32 weeks.

None of the patients had any evidence of cardiovascular disease before or on admission to hospital.

Patients 1 and 3 had twin pregnancies. The membranes were intact in all 4 patients and although patient 4 had pyelonephritis, there was no evidence of chorio-amnionitis in any mother. We do not use tocolysis in patients with evidence of chorio-amnionitis, or abruptio placentae, and rarely in those with ruptured membranes.

On initiation of tocolysis, hexoprenaline 10 μg is given slowly intravenously followed by a titration of 300 μg in 1 litre of normal saline at the lowest rate to suppress uterine activity but not to induce a maternal tachycardia above 120/min. This procedure was followed in each of the 4 cases and the concen-

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TABLE I. SUMMARY OF SALIENT FEATURES OF ALL 4 CASES

	Case 1*	Case 2	Case 3*	Case 4
Age (yrs)	25	29	20	36
Gestation (wks)	32	30	29	28
Blood pressure and pulse rate on admission	120/80;72	110/70;88	110/65;98	115/70;108 (temp. 39°)
Chest radiograph on admission	Clear	Clear	Clear	Clear
Heart, on admission	NAD	NAD	NAD	NAD
Cervical dilatation on admission (cm)	3	1 (cerv. cerclage)	2	2,5
Membranes, on admission	Intact	Intact	Intact	Intact
Chorio-amnionitis, on admission	No	No	No	Pyelonephritis
Full blood count and U&E	Normal	Normal	Normal	Normal
Dose of hexoprenaline (μg/min)	1 - 1,20	0,5 - 1,20	0,5 - 1	0,5 - 1
Betamethasone (mg)	12 × 2	12 × 2	12 × 2	No
Indomethacin (g)	No	1 × 2	1 × 2	No
Tocolysis — pulmonary oedema interval (h)	72	28	56	52
Initial Pao_2	45,8	70	58,2	68,4
Initial $Paco_2$	20,8	40	32,4	40
Chest radiography	Pulm. oedema	Pulm. oedema	Pulm. oedema	Pulm. oedema
ECG	Normal	Normal	Normal	Normal
Positive fluid balance/24 h	1 233	640	780	450
Furosemide (mg)	40 × 3	40 × 2	20 × 2	20 × 1
Delivery	Forceps × 2	C/S	Vaginal	Vaginal
Weight (g)	1 800 1 280	1 500	650 780	1 240
Assisted ventilation	Yes (72 h)	No	No	No
Discharge day	10	7	7	8

* Twin

tration of hexoprenaline infused varied between 0,5 μg and 1,20 μg/min.

Betamethasone 12 mg intramuscularly was given to the first 3 patients on admission and repeated 12 hours later to accelerate fetal lung maturity. Indomethacin was given to patients 2 and 3. This should not exceed 2 g/24 h and is commonly used by two of the authors.

All 4 patients developed dyspnoea, tachypnoea, bilateral basal crepitations and evidence of pulmonary oedema on chest radiography but all had normal ECGs. No significant hypotension or electrolyte disturbance occurred in any of the 4 patients.

The interval from starting hexoprenaline to the time of developing pulmonary oedema varied from 25 hours to 72 hours (average 52 hours).

All patients had a positive fluid balance, the highest positive balance occurring in patient 1 who required assisted ventilation.

Furosemide 20 - 80 mg was given to initiate a diuresis in all patients. A caesarean section for breech presentation was performed in patient 2. Both twin infants of patient 3 died of severe hyaline membrane disease. The other infants all survived after treatment for mild to moderately severe hyaline membrane disease.

Discussion

Pulmonary oedema as a complication of β_2-sympathomimetic treatment to inhibit preterm labour was first reported in 1977.[5] Despite a reported frequency of 5% for this potentially fatal complication[6] there appears to be limited appreciation of the need for cardiovascular monitoring in the mother. Maternal mortality for this complication is in the order of 5 -10%.[7,8]

The pathogenesis of pulmonary oedema associated with tocolytic therapy remains unclear. Cardiac failure does not appear to be the cause of the pulmonary oedema.[9]

During pregnancy there is an increase in pulmonary capillary permeability associated with a decreased plasma oncotic pressure, which results in an increase in total lung water.[10] Beta-sympathomimetic agents appear to increase the alveolar-capillary permeability allowing more fluid into the interstitial lung tissue,[4,9,11] although this is not accepted by all authors.[12]

In addition, β-adrenergic agonists affect total body water balance by stimulating the renin-aldosterone system and releasing antidiuretic hormone, producing an increase in plasma volume and a fall in both haematocrit and colloid osmotic pressure.[13] These effects are most pronounced when isotonic saline solutions are used, resulting in expansion of the plasma volume, producing pulmonary congestion and, in some cases, pulmonary oedema.

Fluid retention due to corticosteroid administration may be important, although betamethasone and dexamethasone have minimal mineralocorticoid activity.

Indomethacin may contribute to sodium and water retention and also affect capillary permeability, although its role in this respect in pregnant women is not clear.[14]

Multiple pregnancy is associated with a greater increase in plasma volume than occurs in singleton pregnancy and is thus predisposed not only to preterm labour, but also to the development of pulmonary oedema when tocolytic agents are used. Two of our 4 cases were in twin pregnancies.

Iatrogenic overload, especially with prolonged intravenous administration of fluids is another contributing factor and in all 4 of our patients a positive fluid balance was recorded, the highest in the most severely affected patient.

In view of our experience, we have instituted guidelines for the use of hexoprenaline tocolysis in preterm labour. On admission to hospital patients with underlying heart disease or evidence of heart disease on ECG examination are excluded from tocolytic therapy with hexoprenaline. Similarly, clinical, biochemical or amniocentesis evidence of chorio-amnionitis excludes patients from tocolysis. In the presence of maternal infection, the risk of pulmonary oedema from tocolytic therapy

is greatly increased.[15,16] If fetal breathing movements are observed on ultrasonography tocolysis is probably not required.

Infusion of hexoprenaline is by titration using 300 μg in 1 litre of half dextrose/saline solution until uterine contractions cease but not exceeding 1,20 μg/min or a maternal pulse rate of 120/min. Intravenous fluid intake is restricted to 125 ml/h and may necessitate doubling the concentration of the hexoprenaline solution. Blood pressure, pulse, temperature, respiration and intake and output are measured hourly. Regular auscultation of the lung bases is performed and if dyspnoea or any signs of pulmonary oedema develop, tocolysis is stopped, blood gases are measured and chest radiography performed. Restarting tocolysis is only considered after careful evaluation of the patient.

The maximum period for which tocolysis is used is 48 hours.

The value of β-sympathomimetic agents appears to be twofold. Firstly, they allow patients to be transferred to hospitals with high-care facilities for the premature infant. Secondly, they allow the administration of corticosteroids where appropriate to enhance fetal lung maturity. Beyond this, there seems very little evidence that sympathomimetic agents will be of benefit in preterm labour. Although randomised clinical trials with β-sympathomimetic agents have produced contradictory results, the majority of well-controlled randomised studies do not show significant prolongation of pregnancy or a significant modification of the ultimate perinatal outcome.[11,17]

It would thus seem that beyond 48 hours any possible benefit will be outweighed by the risks of prolonged use of β-sympathomimetic agents for tocolysis in preterm labour.

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