CASE REPORT

Severe resistant maternal hypotension following tocolysis with nifedipine

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SUMMARY

An 18-year-old woman, gravida 3, para 2, presented at 24 weeks of gestation with preterm premature rupture of membranes. She was started on nifedipine for tocolysis and to facilitate administration of steroids. Two and a half hours later, the patient developed tachycardia and hypotension. Sepsis from chorioamnionitis, acute cardiac event and pulmonary embolism were considered as differential diagnoses. Laboratory and radiological investigations, however, ruled out these possible causes of haemodynamic instability. Her clinical condition deteriorated and hypotension remained intractable despite aggressive fluid resuscitation. An emergency caesarean section at 24 weeks of gestation was carried out in the interest of saving the mother's life. The haemodynamic status of the patient recovered rapidly postcaesarean section. This case report highlights the rare but potentially serious adverse effects of hypotension in administration of nifedipine; and thus reminds us of the importance of judicious prescription and careful titration of nifedipine as a tocolytic.

BACKGROUND

Nifedipine is one of the drugs of choice used regularly for tocolysis during pregnancy. However, it is a calcium channel blocker and carries with it a potential adverse effect of hypotension.

We report a case of severe and resistant hypotension secondary to tocolysis with nifedipine, and briefly review the literature on the adverse effects of nifedipine, how it compares to other tocolytics and refer to other reports of similar presentation.

CASE PRESENTATION

An 18-year-old woman, gravida 3, para 2, presented to the delivery suite, triage, at 24 weeks gestation with a history of leaking liquor. Examination confirmed the diagnosis of preterm premature rupture of membranes (PPROM). She had two previous uncomplicated pregnancies with spontaneous vaginal deliveries. Her present pregnancy had been uneventful to date. There was no significant medical or surgical history of note, including drug allergy.

Following confirmation of diagnosis, the patient was admitted for further monitoring, investigations for chorioamnionitis and management as per local protocol. On admission, she was noted to be afebrile with a pulse rate of 76 bpm and blood pressure of 87/51 mm Hg. Initial investigations revealed normal inflammatory markers.

The patient reported increasing lower abdominal cramps, requiring the use of inhalational entanox for pain relief. In view of the diagnosis of PPROM with risk of a preterm delivery, intramuscular steroids for fetal lung maturity and tocolysis with oral nifedipine were prescribed. At our centre, the two tocolytics available for use are oral nifedipine and intravenous salbutamol. After comparing the side effect profiles of both drugs, the decision was made to start on oral nifedipine, as it was deemed to be the safer option. Intravenous penicillin G and oral erythromycin were also started as per protocol for PPROM. The patient was given a loading dose of nifedipine 10 mg orally (unchewed) every 15 min in four doses. The first dose of the 10 mg nifedipine started at 7:00. The loading dose was completed at 8:00. The patient was scheduled to be placed on a maintenance dose of 20 mg 6 hourly thereafter. Approximately 2.5 h later, at 10:30, the patient reported mild chest tightness. She was afebrile, but her pulse rate was noted to be 135 bpm and blood pressure was 88/43 mm Hg. Her oxygen saturation remained >95% on room air. An ECG and cardiac enzymes did not show any cardiac ischaemia. The planned nifedipine maintenance dose was decreased to 10 mg 6 hourly.

Another 2.5 h later, at 12:00, the patient reported feeling tired and weak. At the same time, it was observed that she was becoming increasingly drowsy. Her pulse rate remained raised at 121 bpm, blood pressure was 83/43 mm Hg.

INVESTIGATIONS

Further investigations were carried out which were all within normal limits. An ECG showed a tachycardia with a normal sinus rhythm. Chest X-ray was unremarkable. Arterial blood gases were normal and did not reveal any acidosis. C reactive protein was 1.3 mg/L, total white cell count was 7.62×10^9/L without any left shift. Procalcitonin level was <0.12 µg/L. Haemoglobin levels were 9.4 g/dL. Clotting profile, liver and renal function tests were normal. Urine and blood cultures were taken and reported no bacterial growth. CK, CKMB and troponin I levels were normal.

DIFFERENTIAL DIAGNOSIS

In view of the history of PPROM, the condition of chorioamnionitis and sepsis had to be considered as a differential diagnosis. The clinical picture of hypotension and tachycardia further increased the suspicion. However, the patient was afebrile and the infectious markers were all within normal limits.

An acute cardiac event was another differential diagnosis, given the fact that the patient was haemodynamically unstable and drowsy. The ECG and cardiac enzymes were normal as well.

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The possibility of a pulmonary embolism had also to be considered, since the patient was pregnant and immobile due to requiring bed rest. She also reported chest tightness. Thus an arterial blood gas test was performed, which was reported to be normal. A chest X-ray was taken, even though these may not be sensitive in diagnosing pulmonary embolism, and was unremarkable.

Allergic reactions to drugs could also manifest with low blood pressure. However, the patient had previously taken penicillins with no allergic reactions and is not known to have allergy to other medications.

TREATMENT

The patient was fluid resuscitated with 1.5 L of crystalloids and 500 mL of colloids. Antibiotics were escalated to broad spectrum intravenous antibiotics to cover Gram-positive and Gram-negative organisms, as well as anaerobes. The anaesthesiologists were consulted and the patient was managed in a high dependency setting.

However, her heart rate remained at 120–130 bpm, and she became increasingly drowsy and unresponsive. About 7 h after the initial nifedipine dose, at 14:00, her blood pressure dropped to 76/42 mm Hg, and the heart rate escalated to 140 bpm. Oxygen saturations, however, remained at 100% on a 2 L face mask.

In view of the deteriorating haemodynamic status, which was unresponsive to aggressive fluid resuscitation, as well as the rapidly declining mental state, the decision was taken to deliver the patient via an emergency caesarean section, as a lifesaving measure.

OUTCOME AND FOLLOW-UP

The patient received a general anaesthetic for the procedure, which was uneventful. Prior to induction of anaesthesia in the operating theatre, the patient's blood pressure dropped to a low of 56/43 mm Hg. Intraoperatively, there was no sign of placental abruption, bleeding or any intra-abdominal source of sepsis.

The blood pressure stabilised to 100/60 mm Hg within 30 min of delivery of the baby. The heart rate had settled to 98 bpm. Thereafter, the blood pressure was maintained above 100/60 mm Hg with a maintenance drip and without the need for any inotropes. Notably, post section, the patient's drowsiness had resolved and she became alert and orientated. She was placed on prophylactic intravenous antibiotics post-caesarean section and this was oralised on the third postoperative day. Her recovery was smooth and uneventful and she was discharged on the fourth postoperative day.

DISCUSSION

Nifedipine is a dihydropiridine calcium channel blocker and works by blocking L-type calcium channels, thereby inhibiting the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is licensed as an antihypertensive, and its mechanism of action involves peripheral arterial vasodilation, consequently reducing peripheral vascular resistance.

These L-type calcium channels are also found in the uterine myometrium and calcium flux is essential for excitation–contraction coupling to occur in the pregnant uterus.[1] Thus nifedipine has also been long used as a uterine tocolytic and, in fact, its efficacy has been found to be equal to or better than those of β-agonists and oxytocin antagonists.[2] Meta-analyses and randomised controlled trials comparing nifedipine and ritodrine have found that nifedipine is more effective with less maternal side effects and improved neonatal outcomes.[3–6] In addition, it is inexpensive and its oral formulation makes it convenient to administer.

However, nifedipine, when used as a tocolytic, not unexpectedly may cause side effects of hypotension and tachycardia, especially when it is administered at higher doses or in a chewed or sublingual form. In a single centre randomised controlled trial comparing three tocolytics, Klauser *et al*[7] found that there were significantly more patients with hypotension and tachycardia among those who received nifedipine compared to those who received indomethacin or magnesium sulfate.

Irregardless, nifedipine is, in general, still considered a safe drug as the incidences of maternal tachycardia, hypotension and fetal tachycardia are low. In fact, the Royal College of Obstetricians and Gynaecologists Guideline No 1b recommends that nifedipine or atosiban be used as preferred first-line tocolytics, in preference to β-sympathomimetics, as the former two are more effective and cause fewer maternal side effects.[8]

In one study, it was found that the incidence of profound maternal hypotension (<80/50 mm Hg) that necessitated discontinuation of nifedipine was 1%.[9] The hypotensive episodes occurred about 2 h after the start of therapy. Other side effects included flushing, headache, nausea and dizziness; and the incidence of these side effects ranged from 1% to 4%.

Although the incidence of profound hypotension is relatively low, it is important to be mindful of such a potential adverse effect. In extreme cases, the hypotension can be so intractable that it leads to abnormalities in the cardiotocograph, fetal distress and even ultimately fetal demise.[10] Thus, if hypotension occurs, fluid resuscitation must be started immediately to avert further adverse consequences. The elimination half-life of nifedipine is approximately 2 h, but in one case[10] it was reported that the blood pressure only reached its normal levels 6 h after fluid resuscitation.

Our case illustrates the potential adverse consequence of refractory hypotension when administering nifedipine that has to be borne in mind. As a result, nifedipine as a tocolytic should be used judiciously only when there is a certain indication. Also, because of the rarity of this condition, it will be difficult to predict which patients will develop such extreme hypotension in response to nifedipine. Thus, as nifedipine is being prescribed, it is advised to monitor the blood pressure very closely and consider omitting subsequent doses if the blood pressure is too low.

However, as illustrated in this case, even with monitoring of the blood pressure, the patient could abruptly deteriorate. In such a scenario, the patient must be carefully managed in partnership with the intensivists. With the benefit of hindsight, perhaps, if this patient had been stabilised with vasopressors, we might have been able to sustain her through the acute hypotensive event until the nifedipine was cleared from her system, since her clinical status returned to normal within 30 min of delivery of the baby. However, in the light of a rapidly deteriorating clinical status, there was suspicion of an attributable pathology, such as sepsis or concealed placental abruption, thus the decision was taken to deliver the baby as a life-saving measure for the patient. On delivery, there was no other specific cause found for the hypotension, and the quick return of the blood pressure to normal was most probably because the drug had been cleared out of the system by then.

Therefore, this case report would be extremely helpful to fellow clinicians who in future might come across similar clinical scenarios and to inform fellow colleagues about the possibility of this potential rare complication, so that they would be suitably informed to better manage their patients.

Learning points

- Nifedipine is frequently a tocolytic of choice given its favourable side effect profile, ease of use and cost-effectiveness. However, it should nonetheless be used judiciously and only when there is a definite indication.
- Nifedipine, when used as a tocolytic, has the potential to cause severe hypotension resistant to aggressive fluid resuscitation.
- The dosage of nifedipine should be titrated carefully beginning with the lowest required dose.

Competing interests None.

Patient consent Obtained.

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