Case Reports in Women's Health 25 (2020) e00173

Contents lists available at ScienceDirect

Case Reports in Women's Health

journal homepage: www.elsevier.com/locate/crwh

Maternal pulmonary edema after 46 h of ritodrine hydrochloride administration: A case report

Tsuyoshi Murata *, Hyo Kyozuka, Aya Shiraiwa, Hirotaka Isogami, Toma Fukuda, Aya Kanno, Akiko Yamaguchi, Keiya Fujimori

Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, Fukushima, Japan

ARTICLE INFO

Article history:
Received 22 December 2019
Received in revised form 7 January 2020
Accepted 10 January 2020
Available online xxxx

Keywords:
Ritodrine hydrochloride
Pulmonary edema
Magnesium sulfate
Betamethasone

ABSTRACT

Introduction: Ritodrine hydrochloride is still widely used as a tocolytic agent in Japan, but it can cause maternal pulmonary edema, which may paradoxically induce preterm birth. Here we present a case of severe pulmonary edema due to <48 h of ritodrine administration.

Case: A 46-year-old woman was diagnosed with threatened preterm labor (TPL) and placenta previa at 26 weeks of gestation. She had mild uterine contractions and genital bleeding. Ritodrine hydrochloride, magnesium sulfate, and betamethasone were administered. She developed dyspnea 46 h after starting ritodrine administration. Chest X-ray showed pulmonary edema. Even after cessation of ritodrine, dyspnea did not lessen and there were regular uterine contractions with abdominal pain. Emergency caesarean section was performed. A female neonate was delivered and admitted to the neonatal intensive care unit. After surgery, maternal dyspnea decreased without any complications.

Discussion: Excessive use of ritodrine or its use in combination with other tocolytic agents can cause maternal pulmonary edema, even with <48 h of use. Adverse maternal side-effects and rebound uterine contractions due to cessation of ritodrine may paradoxically trigger preterm birth. Strict patient selection for tocolytic therapy is essential and ritodrine requires caution because of its potential side-effects.

1. Introduction

Ritodrine hydrochloride is a beta-sympathomimetic agent used in preterm labor. It predominantly interacts with beta-2 receptors of the uterus [1]. Ritodrine is still widely used as a tocolytic agent in Japan. However, ritodrine often causes adverse maternal side-effects such as pulmonary edema, granulocytopenia, and rhabdomyolysis [2] [3]. Although beta-sympathomimetics are indeed effective in prolonging pregnancy for 48 h according to a 2012 network meta-analysis [4], pulmonary edema can occur before 48 h. Due to such severe side-effects, ritodrine is often switched to other medications [4]; however, cessation of intravenous ritodrine often causes regular uterine contractions. Adverse maternal side-effects and rebound uterine contractions may paradoxically lead to preterm birth.

Here we present a case in which ritodrine administration for <48 h caused severe maternal pulmonary edema, paradoxically induced rebound uterine contractions, and led to preterm birth at 26 weeks of gestation.

2. Case Presentation

A healthy, non-smoking, multiparous, 46-year-old woman became aware of mild uterine contractions and genital bleeding. Cardiotocography demonstrated regular uterine contractions and reassuring fetal status. Ultrasound sonography showed placenta previa without cervical shortening. She was diagnosed with threatened preterm labor (TPL) due to regular uterine contractions. She was admitted to the obstetric unit. She did not have a history of preterm birth with her other pregnancies. The fetus appeared to have an appropriate estimated body weight and no structural anomalies. Intravenous ritodrine was administered at 100 μg/min, intravenous magnesium sulfate was administered at 1 g/h, as a tocolytic agent and a neuroprotective agent, respectively. Betamethasone (12 mg/day) was also administered for 2 days as antenatal corticosteroid therapy. Because uterine contractions did not lessen over the next day, ritodrine was increased to 133 μg/min, and 500 ml/2 h of physiological saline was infused for hydration. We did not detect changes in the length of the uterine cervix.

Forty-six hours after starting ritodrine, the patient developed dyspnea at rest. Dyspnea did not resolve and oxygen saturation was 94% while breathing room air. Chest X-ray showed a butterfly pattern of acute pulmonary edema and a cardiothoracic ratio of 53% (Fig. 1). The patient did not have hypertension. The brain natriuretic peptide level

* Corresponding author at: 1, Hikarigaoka, Fukushima city 960-1295, Japan.
E-mail address: tuyoshim@fmu.ac.jp (T. Murata).

https://doi.org/10.1016/j.crwh.2020.e00173

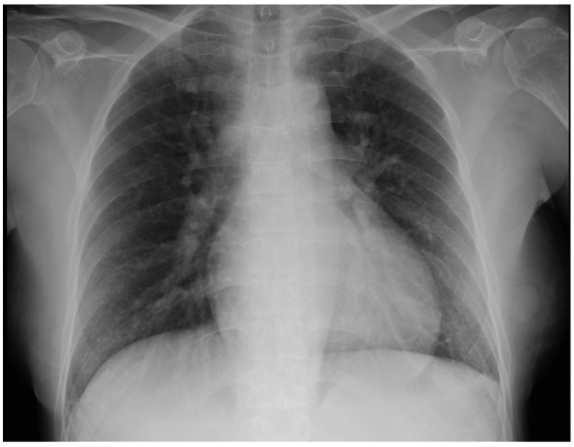

Fig. 1. Chest X-ray showed a butterfly pattern of acute pulmonary edema and the cardio thoracic ratio was 53%.

of 160.9 pg/ml (normal range: <18.4 pg/ml) indicated acute heart failure. Echocardiography showed acute pulmonary hypertension but no signs of pulmonary thromboembolism or deep-vein thrombosis. Therefore, we diagnosed circulatory changes induced by ritodrine. After cessation of ritodrine, dyspnea did not lessen and there were regular uterine contractions with abdominal pain.

An emergency caesarean section was performed at 26 weeks of gestation due to maternal pulmonary edema and rebound uterine contractions. There was a small amount of maternal ascites. A female neonate was delivered (950 g, Apgar score at 1 and 5 min: 4 and 6, respectively). Dyspnea lessened after surgery and pulmonary edema resolved on chest X-ray 4 days after surgery (Fig. 2). The patient was discharged 6 days after surgery without any complications.

The neonate was admitted to the neonatal intensive care unit and diagnosed with respiratory distress syndrome. She was discharged 98 days after admission, without any complications.

3. Discussion

Excessive use of ritodrine or the combination of ritodrine with other tocolytic agents, antenatal corticosteroids, and hydration is associated with the risk of maternal pulmonary edema, even with <48 h of use. Adverse maternal side-effects and rebound uterine contractions due to cessation of ritodrine may paradoxically trigger preterm birth.

Tocolytic agents must be used properly in patients diagnosed with TPL. Strict indications for the use of tocolytic agents in TPL should be observed because of its potential side-effects. The objective of tocolysis is prolongation of pregnancy by at least 48 h to ensure completion of antenatal corticosteroid therapy and to enable in-utero transfer of the pregnant woman to a perinatal center [5] [6]. There are several recommendations regarding the use of tocolytic agents. For example, the American College of Obstetricians and Gynecologists recommended the use of tocolytic agents when there are regular preterm contractions and cervical dilation is ≥2 cm [5]. According to the current recommendations of the European Association of Perinatal Medicine, tocolysis is indicated at the onset of regular preterm contractions (not fewer than 4 contractions within 20 min) and dynamic cervical changes [6].

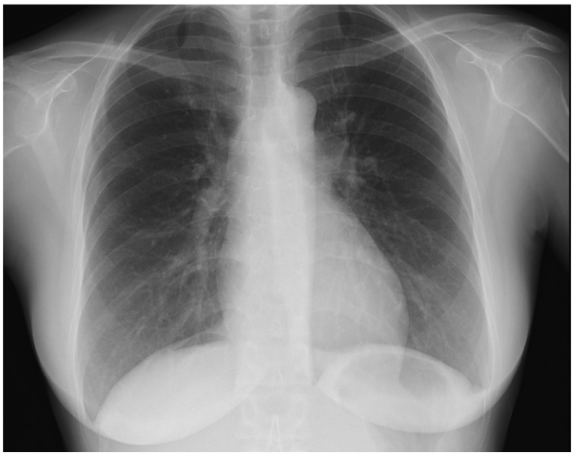

Fig. 2. Pulmonary edema resolved on chest X-ray 4 days after surgery.

Although previous reports have not shown the effectiveness of long-term tocolysis [4], and given the disadvantages of ritodrine use as a tocolytic agent [2], there may be a gap between available evidence and actual clinical practice for preterm birth in Japan [3]. In Japan, TPL is diagnosed on the basis of regular uterine contractions and cervical dilatation or shortening of the cervical length [7]. In addition, Japanese guidelines do not exclude the use of ritodrine, based on a limited study that demonstrated the effectiveness of long-term tocolysis with ritodrine [8]. Moreover, nifedipine, a safe and inexpensive tocolytic agent used all over the world, cannot be used as standard therapy in Japan because nifedipine is not included in the universal healthcare coverage for threatened preterm labor [3]. With regard to clinical indications, prophylactic tocolysis and treatment for physiological uterine contractions during pregnancy that have no effect on the cervix frequently turn out to be unnecessary and even harmful [9].

Ritodrine, which is a beta-2 adrenergic agonist that relaxes the uterus by stimulating beta-2 adrenergic receptors in the uterine smooth muscle cells [1], stimulates beta-adrenergic receptors in bronchial and vascular smooth muscle cells, which are related to most of its adverse effects, such as pulmonary edema, tachycardia, and hypertension [9]. The cause of pulmonary edema is multifactorial. Risk factors include tocolysis for >24 h, concurrent corticosteroid therapy, infusion of large volumes of intravenous crystalloid, and multifetal gestation [10]. Pulmonary edema associated with ritodrine can be increased with other tocolytic agents or betamethasone [11,12] as well as excessive intravascular fluid administration, cardiac failure, or pulmonary capillary endothelial damage [13]. Leveno and Cunningham reported pulmonary edema in 3–9% of cases with ritodrine [14]. However, a previous Japanese report showed that the prevalence of pulmonary edema with <48 h of ritodrine therapy was 1.2% and 0.06% if ritodrine was used for >28 days [3]. Furthermore, cessation of ritodrine due to adverse maternal side-effects can cause rebound uterine contractions and sometimes lead to preterm birth. A retrospective cohort study showed that 4.2% of patients who receive intravenous ritodrine require cessation due to severe maternal side-effects such as pulmonary edema [15].

In conclusion, ritodrine often causes adverse maternal side-effects and rebound uterine contractions, even with <48 h of administration, as in this case. These conditions may paradoxically trigger preterm labor. Strict patient selection for tocolytic therapy is essential and the use of ritodrine requires caution because of its potential side-effects.

Contributors

All authors were involved in the clinical care of the patient and contributed to the conception, drafting, review, and revision of the manuscript. All authors read and approved the final version of the paper and take full responsibility for the work.

Conflict of Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Funding

This work did not receive any specific grants from funding agencies.

Patient Consent

Informed consent was obtained from the patient for publication of this work.

Provenance and Peer Review

This case report was peer reviewed.

References

[1] T.P. Barden, J.B. Peter, I.R. Merkatz, Ritodrine hydrochloride: a betamimetic agent for use in preterm labor. I. pharmacology, clinical history, administration, side effects, and safety, Obstet. Gynecol. 56 (1980) 1–6.

[2] J.P. Neilson, H.M. West, T. Dowswell, Betamimetics for inhibiting preterm labour, Cochrane Database Syst. Rev. 5 (2014), CD004352.

[3] D. Shigemi, S. Aso, H. Yasunaga, Inappropriate use of ritodrine hydrochloride for threatened preterm birth in Japan: a retrospective cohort study using a national inpatient database, BMC Pregnancy Childbirth. 19 (2019), 204.

[4] D.M. Haas, D.M. Caldwell, P. Kirkpatrick, J.J. McIntosh, N.J. Welton, Tocolytic therapy for preterm delivery: systematic review and network meta-analysis, BMJ. 345 (2012) e6226.

[5] American College of Obstetricians and Gynecologists" Committee on Practice Bulletins—Obstetrics, Practice bulletin no. 171: Management of Preterm Labor, Obstet. Gynecol. 128 (2016) e155–e164.

[6] G.C. Di Renzo, L. Cabero Roura, F. Facchinetti, H. Helmer, C. Hubinont, B. Jacobsson, J.S. Jørgensen, R.F. Lamont, A. Mikhailov, N. Papantoniou, V. Radzinsky, A. Shennan, Y. Ville, M. Wielgos, G.H.A. Visser, Preterm labor and birth management: recommendations from the European Association of Perinatal Medicine, J. Matern. Fetal Neonatal Med. 30 (2017) 2011–2030.

[7] Japan Society of Obstetrics and Gynecology and Japan association of Obstetricians and Gynecologists, Guidelines for Obstetrical Practice in Japan 2017, 2017 152–157 edition.

[8] K. Takagi, K. Satoh, Is long-term tocolysis effective for threatened premature labour? J. Int. Med. Res. 37 (2009) 227–239.

[9] A. Wischnik, Risk-benefit assessment of tocolytic drugs, Drug Saf. (5) (1991) 371–380.

[10] F.G. Cunningham, K.J. Leveno, S.L. Bloom, J.S. Dashe, B.L. Hoffman, B.M. Casey, C.Y. Spong, Williams OBSTETRICS, Twenty Fifth Mc-Graw Hill Education, New York, 2018.

[11] P.L. Ogburn Jr., T.M. Julian, P.P. Williams, T.R. Thompson, The use of magnesium sulfate for tocolysis in preterm labor complicated by twin gestation and betamimetic-induced pulmonary edema, Acta Obstet. Gynecol. Scand. 65 (1986) 793–794.

[12] A. Pou-Martinez, S.H. Kelly, F.D. Newell, C.M. Culbert, Postpartum pulmonary edema after ritodrine and betamethasone use, J. Reprod. Med. 27 (1982) 428–430.

[13] G.J. Clesham, Beta adrenergic agonists and pulmonary oedema in preterm labour, BMJ. 308 (1994) 260–262.

[14] K.J. Leveno, F.G. Cunningham, Beta-adrenergic agonists for preterm labor, N. Engl. J. Med. 327 (1992) 349–351.

[15] M.K. Kim, S.M. Lee, J.W. Oh, S.Y. Kim, H.G. Jeong, S.M. Kim, C.W. Park, J.K. Jun, S.K. Hahn, J.S. Park, Efficacy and side effect of ritodrine and magnesium sulfate in threatened preterm labor, Obstet. Gynecol. Sci. 61 (2018) 63–70.