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Intravenous acetaminophen for the treatment of intrapartum fever and resolution of fetal tachycardia: a novel use for an old medication

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Summary

This case series demonstrates a potential new role for the use of intravenous (IV) acetaminophen. The authors reviewed two cases, whereby patients that developed intrapartum fever leading to fetal tachycardia were effectively treated with IV acetaminophen, leading to rapid reduction of maternal temperature and resolution of fetal tachycardia. Both patients had an uncomplicated vaginal delivery of healthy neonates. Intravenous acetaminophen, with its increased bioavailability and more rapid onset of action, may have benefit in the intrapartum setting by reducing adverse neonatal and maternal outcomes associated with febrile morbidity.

Key words: Intravenous acetaminophen; Intrapartum fever; Fetal tachycardia.

Introduction

Among the four million deliveries that take place yearly in the United States, about 7% of term births are affected by maternal fever [1]. Causes of intrapartum fever have been attributed to both infectious and non-infectious origin, including, epidural use, oxidative stress, and chorioamnionitis [2]. Factors associated with increased risk of intrapartum fever include maternal age, nulliparity, induction of labor, and a longer laboring process [3]. Both infectious and non-infectious etiologies of maternal fever have been linked to neonatal complications such as low Apgar scores, respiratory distress, need for mechanical ventilation, hypotonia, cerebral palsy, encephalopathy, neonatal seizures, and neonatal death [1-3]. Another consequence of maternal fever is its effect on the fetal heart rate. Studies have demonstrated a correlation between maternal fever and the development of fetal tachycardia [4]. Fetal tachycardia, caused by maternal hyperthermia, may necessitate a cesarean delivery secondary to a persistent non-reassuring fetal heart status remote from delivery. Therefore, rapid resolution of maternal fever and fetal tachycardia has the potential to reduce adverse maternal and neonatal outcomes associated with febrile morbidity.

Compared to oral acetaminophen, intravenous acetaminophen has increased bioavailability and more rapid onset of action [5]. IV acetaminophen has been used successfully in the management of fever in postoperative patients [6, 7]. Additionally, intravenous acetaminophen has also been used in the intrapartum setting for management of pain [8]. However, the use of intravenous acetaminophen for the treatment of maternal temperature and subsequent resolution of fetal tachycardia, has not yet been evaluated.

Case Report

Case 1

A 25-year-old gravida 1 para 0 at 40 weeks and 3 days gestation presented to the obstetrical triage unit an hour and half after an episode of leakage of fluid from the vagina. She had an uncomplicated pregnancy, and denied previous surgery or any medical condition. The patient was afebrile and in no acute distress. A complete blood count showed a white count of 16.5 x 10^9/L; abdominal examination revealed a non-tender abdomen and gravid uterus corresponding to 40 weeks gestation. Vaginal examination confirmed membrane rupture. The cervix was two-cm dilated, 80% effaced, and the fetal head was at station -2. The fetal heart tracing was Category I, with baseline FHR at 145 beats per minute. External tocography showed irregular contractions.

The patient was admitted for rupture of membranes and her labor was augmented with oxytocin. Epidural was placed for pain management. Ten hours after membrane rupture, the patient developed a low grade temperature of 37.9°C and the fetus had tachycardia (FHR baseline 180 bmp) with moderate variability. Maternal heart rate was 84 bpm and there was no uterine tenderness or vaginal discharge. The cervix was seven-cm dilated, 90% effaced, and the fetal head was at station -2.

An oral dose of 650 mg acetaminophen was initially administered along with intravenous ampicillin and gentamicin with no improvement in fetal tachycardia. The maternal temperature increased to 38.1°C and 38.4°C after one and two hours of administration of oral acetaminophen respectively. Intravenous acetaminophen (1,000 mg) was then administered. After 20 minutes, the maternal temperature normalized to 37.0°C with reduc-

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tion in FHR to 160 beats per minute. The patient had an uneventful vaginal delivery of 3,238 grams baby with one- and five-minute Apgar scores of 9 and 9, respectively, an hour and a half after the administration of intravenous acetaminophen. The baby was initially observed in the neonatal intensive care unit (NICU) to rule out sepsis secondary to the presence of maternal fever. All laboratory evaluation and blood cultures were negative.

Case 2

A 26-year-old gravida 2 para 0 at 38 weeks and five days gestation presented to labor and delivery with complaint of spontaneous rupture of membranes that occurred one hour previously. She had a normal obstetric course with this pregnancy, with no contributory medical or surgical history. On initial presentation, she was afebrile. Physical examination confirmed membrane rupture. The cervix was three-cm dilated, 80% effaced, and the fetal head was at station -2. The fetal heart tracing was Category I, with base line at 130 beats per minute. External tocography showed irregular contractions every five to seven minutes.

She was administered oxytocin for augmentation of labor. Ten hours after membrane rupture and within 45 minutes of epidural administration, the patient developed a temperature of 38.1°C, with maternal heart rate of 89 beats per minute. The baseline FHR was 190 beats per minute with moderate variability. There was no uterine tenderness or vaginal discharge, and her cervix was five-cm dilated, 80% effaced, and fetal head was at -2 station. Intravenous acetaminophen (1,000 mg) was administered. After 20 minutes, the maternal temperature was reduced to 37.5°C with resolution of the fetal tachycardia to a baseline of 160 beats per minute. The patient was able to continue with labor, and three hours after the administration of intravenous acetaminophen, had a vaginal delivery of a 3,538 grams neonate with 9 and 9 Apgar scores at one and five minutes. Both blood cultures and placental histology were negative for chorioamnionitis.

Discussion

The presence of a maternal intrapartum fever can have serious consequences for both the mother and the fetus. The advantage of using intravenous acetaminophen in the intrapartum setting is its rapid onset of action, which may allow for the prevention of fetal temperature elevations following maternal fever. Primate studies have demonstrated that maternal fever in the absence of infection has been directly associated with the development of neonatal hypoxia and metabolic acidosis [9]. Even a one to two degree Celsius elevation in fetal brain temperature can potentiate brain damage resulting from an ischemic insult [9]. Maternal oral temperature values underestimate fetal brain temperature by an average of 0.8 degrees Celsius. Therefore, with a maternal temperature of 38 degrees Celsius (the lower threshold for defining intrapartum fever), fetal brain temperature may reach 39.5 degrees Celsius or higher [10,11]. This elevation in fetal brain temperature may potentiate fetal neurological injury, especially in the presence of hypoxia.

Term infants have a low risk of encephalopathy of approximately 0.12%. The observed risk of encephalopathy increases when the fetus is exposed to maternal fever alone (1.13%) or with the presence of acidosis alone (1.58%) [10]. When both maternal fever and acidosis co-exist, the observed risk of encephalopathy greatly increases to 12.5%, independent of neonatal sepsis [3, 10]. Therefore, rapid correction of maternal intrapartum fever may be a critical step in reducing neonatal morbidity.

The safety profile, pharmacokinetics and pharmacodynamics of intravenously administered acetaminophen are favorable when compared to equivalent doses administered orally or rectally [5]. The mean peak plasma concentration (C_{max}) of an intravenous infusion of acetaminophen is 70% higher than a similar oral dose. The median time to reach peak plasma concentration (T_{max}) with IV administration of acetaminophen is 15 minutes, compared to 45-75 minutes for oral, and three to four hours for rectal administration [12]. The higher plasma concentration that results from intravenous administration remains below the level that could potentially be hepatotoxic. Intravenous administration has the additional benefit of avoiding first-pass hepatic metabolism, thereby reducing the hepatic exposure two-fold compared to oral administration [12].

Although intravenous acetaminophen is now commonly accepted as a treatment for postoperative pain, its effect as an anti-pyretic agent has also been well characterized. Peacock *et al*. randomized 105 patients with endotoxin-induced fever to receive either IV acetaminophen one gram versus oral acetaminophen one gram over a six-hour period. The study found that a single dose of IV acetaminophen was as safe and effective at reducing temperature elevation compared to the oral dose, with decreased incidence of vomiting in the IV group [6]. Another randomized study performed by *Kett et al*. compared IV administration of acetaminophen with an IV placebo to assess the treatment related side effects in 60 patients using an endotoxin induced fever model [7]. The study demonstrated that IV acetaminophen effectively reduced fever and was well-tolerated, with frequency of adverse events comparable to that of IV placebo [7].

Acetaminophen is considered safe in pregnancy and intravenous administration has been evaluated in laboring patients for pain control without any adverse maternal or neonatal effects [8, 13]. In addition, IV administration may be a more appropriate route for laboring patients as some may not be able to tolerate oral intake secondary to nausea and vomiting. Rectal administration has difficulties including increase chance of expulsion during pushing, and lower C_{max} compared to the oral or IV routes.

The case series presented highlights a potential new role for the use of intravenous acetaminophen for the management of intrapartum maternal fever. The patient in case 1 had temperature elevations that were refractory to oral acetaminophen administration. Due to the non-responsiveness of the initial treatment with oral medication and the persistence of fetal tachycardia, cesarean delivery was considered. After intravenous administration of acetaminophen, there was a rapid reduction of maternal temperature with resolution of fetal tachycardia. Consistent with

the T_{max} of IV acetaminophen, both patients experienced reduction of maternal temperature and resolution of fetal tachycardia after 20 minutes of administration of IV acetaminophen. There was no incidence of maternal or neonatal culture positive for sepsis or infection in this series and no adverse events secondary to intravenous acetaminophen administration were observed.

In the two cases described, resolution of maternal fever and subsequent fetal tachycardia led to the prevention of cesarean delivery secondary to a non-reassuring fetal heart rate status. Absence of maternal fever at the time of delivery also prevented admission to the NICU (to exclude for possible neonatal sepsis) and associated costs. In both cases, the maternal fever was most likely associated with epidural administration and prolonged rupture of membranes.

Conclusion

The authors hypothesize that intrapartum administration of intravenous acetaminophen for maternal fever can more rapidly and effectively correct maternal pyrexia. This could subsequently resolve fetal tachycardia associated with increased maternal temperature, and potentially decrease the number of cesarean deliveries performed for non-reassuring fetal heart rate status. As a secondary outcome, correction of intrapartum temperature may lead to a reduction in the number of NICU admissions secondary to presence of maternal fever at delivery. Further randomized trials are needed to evaluate the efficacy, maternal morbidity, cesarean delivery rate, and neonatal outcomes of treatment with intravenously versus orally administered acetaminophen.

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