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Case Report

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Severe Hyperthermia With Altered Mental Status After Misoprostol Administration: Two Case Reports

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Abstract

Misoprostol's low cost and temperature stable profile lends itself to widespread usage for postpartum hemorrhage (PPH). A common side effect is fever; however, this more rarely can present as a profound fever with altered mental status. We present two patients who received misoprostol for PPH, after which both had severe hyperthermia and altered mental status and were managed with sepsis protocol and anticonvulsants. These cases illuminate the importance of treatment selection in the management of uterine atony and subsequent steps of care of severe hyperthermia given the risk for adverse events. There needs to be awareness of this uncommon complication with administration of misoprostol. Supportive care and inclusion of the medication adverse effect in the broad differential are essential during presentation of the rare event of severe hyperthermia with altered mental status. It is important to be aware of this adverse effect with administration of more than 600 µg of misoprostol in the setting of PPH.

Keywords: Labor; Uterine atony; Medication; Hyperthermia

Introduction

Postpartum hemorrhage (PPH) occurs with 3.0% of deliveries globally, with increasing rates between 2000 and 2019 [1]. Misoprostol, a prostaglandin E1 derivative, has been used as a low-cost, ambient-temperature stable option for PPH, especially where resources to administer conventional parenteral uterotonics are scarce [2]. Common side effects of misoprostol include nausea, abdominal pain, shivering, and fever [3]. However, few reports have discussed severe hyperthermia and altered mental status.

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Case Reports

Case 1

A 34-year-old gravida 1 presented at 36 + 3/7 weeks for scheduled induction of labor for intrahepatic cholestasis of pregnancy, diagnosed at 31 weeks by pruritis with total bile acids of 20.5 µmol/L and mildly elevated aspartate aminotransferase (AST) of 84 U/L and alanine aminotransferase (ALT) of 75 U/L. Her pregnancy was also complicated by preeclampsia without severe features, diagnosed at 32 weeks by mild range blood pressures with urine protein-to-creatinine ratio of 0.4. AST/ALT were mildly elevated and on serial lab draws weekly did not exceed two times the upper limit of normal, and all other preeclampsia labs were normal. On admission, labs included normal white blood cell count (6.18×10^3/µL), hemoglobin (12.0 g/dL), platelet count (222×10^3/µL), and creatinine (0.55 mg/dL). AST/ALT were elevated at 77 U/L/41 U/L.

Labor was induced with one dose of buccal misoprostol 50 µg with concurrent use of 60 mL transcervical balloon. Following spontaneous expulsion of the balloon, the patient requested and received a labor epidural. Labor was augmented with oxytocin infusion and amniotomy. During induction and labor, patient was afebrile without tachycardia, and her blood pressures were intermittently elevated in the mild range (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg). Oxytocin was infused for a total of 6 h 21 min, to a maximum of 10 milliunits/min. Time from amniotomy to delivery was 3 h 16 min. Patient pushed for 5 min and delivered an infant with Apgars 8/9. Placenta spontaneously delivered intact 4 min later. A second-degree perineal laceration was repaired in the standard fashion using 2-0 polysorb suture. Quantitative blood loss (QBL) was 500 mL, due to intermittent uterine atony, for which the patient received a 60-unit bolus of intravenous (IV) oxytocin, intramuscular carboprost tromethamine 250 µg, buccal misoprostol 800 µg, and intravenous tranexamic acid 1,000 mg bolus.

Approximately 1 h after delivery, the patient became febrile to 41.1 °C with tachycardia of 124 bpm. She reported subjective fever, chills, and shivering. She denied headache, vision changes, chest pain, shortness of breath, and abdominal pain. Blood pressure was normal at 137/83 mm Hg. Oxygen saturation on room air was 97%. Physical exam revealed the patient to be in moderate distress with shivering and to have tachycardia without murmurs, clear lungs on auscultation,

uterine fundus firm at umbilicus without tenderness, normal postpartum lochia, 2+ patellar reflexes, and no ankle clonus. Tests ordered included a sepsis lactate, blood cultures, urine culture, repeat coronavirus disease (COVID) swab, and complete blood count (CBC) with differential.

While awaiting lab results, initial interventions included oral acetaminophen 1,000 mg, 1 L bolus of lactated Ringers, and cooling measures. We initiated IV ampicillin and gentamicin for presumed intra-amniotic infection. Lab results notable for white blood cell (WBC) was 12 × 10^3/µL with left shift and an initial lactate of 34 mg/dL. Subsequently, the patient became altered and non-verbal, though she remained responsive to commands. A rapid response and code stroke was alerted. The patient's temperature was 42.0 °C. Electrocardiogram (ECG) showed sinus tachycardia at 118 bpm. Her neurological examination was without focal deficits. We started IV magnesium for concern of eclampsia with possible nonconvulsive seizure and administered IV lorazepam 1 mg with some mental status improvement. The patient was then transferred to an intensive care unit (ICU) for further management.

Thirty minutes after lorazepam administration, the patient's fever down trended to 38.9 °C. Her mental status improved and she was alert and responsive, though she had no recollection of prior events, including the delivery of her baby. Brain computed tomography (CT) and chest X-ray were both unremarkable. Laboratory values were also unremarkable, with lactate normalizing at 7 mg/dL. Blood and urine cultures were negative. Cooling measures were maintained, and the patient's vitals normalized.

The patient was transferred out of the ICU on postpartum day 1. The remainder of her postpartum course was unremarkable and she was ultimately discharged home on postpartum day 2.

Case 2

A 33-year-old gravida 1 presented for induction of labor for late term gestation at 41 + 0/7 weeks. Patient was a Jehovah's Witness and declined blood products, but was amenable to cell saver, albumin, intravenous immunoglobulin (IVIG), and clotting factors.

Her induction started with buccal misoprostol 50 µg. She received four serial doses, 4 h apart. Membranes spontaneously ruptured after fourth dose and cervical examination was 1 cm dilated, 80% effaced, at -1 station. Contractions were regular and the patient was expectantly managed. She made appropriate cervical change and oxytocin augmentation was initiated at 6 cm dilation. Titration of oxytocin was limited in the setting of category II tracing with minimal variability and intermittent variable and late decelerations. After 5 h and 34 min, the patient entered second stage of labor. Patient pushed for approximately 2 h with a fetal heart rate tracing (FHT) notable for minimal variability with progressively worsening prolonged late decelerations. Recommendation was made for vacuum-assisted vaginal delivery.

Vacuum-assisted vaginal delivery was successful after three contractions, including one pop off, a right mediolateral episiotomy, and Ritgen's maneuver. Infant was vigorous with Apgars of 8/9. Placenta was delivered spontaneously intact after 2 min. A second-degree perineal tear and bilateral sulcal tears were repaired with 2-0 polysorb suture. Uterine atony was actively managed with intramuscular methylergometrine 200 µg, intramuscular carboprost tromethamine 250 µg, IV tranexamic acid (TXA) 1,000 µg, and rectal misoprostol 1,000 µg. QBL was 500 cc.

Patient was hemodynamically stable during initial recovery. She had a temperature of 37.4 °C, blood pressure of 110/80s, and heart rate of 80 bpm. Approximately 2 h after delivery, the patient became non-verbal, intermittently agitated, and was not alert or oriented to person, place, or time. She responded to voice and painful stimuli. Her temperature at this time was 39.2 °C, tachycardic 159 bpm, and tachypneic 27. Blood pressure was unable to be obtained. No convulsive activity was noted. Lungs were clear and lochia was within normal limits. Labs drawn included sepsis lactate, blood cultures, urine culture, CBC with differential, complete metabolic panel, and coagulation panel. Rapid response was alerted. Initial interventions included cooling measures, IV lactated Ringers 1 L, and IV acetaminophen 1,000 mg. We started empiric antibiotics with IV ampicillin, gentamicin, and clindamycin for presumed sepsis. Decision was made to transfer patient to the ICU for further management.

Patient's mental status gradually improved after the above interventions; however, she continued to have intermittent episodes of obtundation. She subsequently developed episodes of emesis. Labs were notable for WBC 27 × 10^3/µL and lactate 42 mg/dL. Urine and blood cultures were negative. Chest X-ray, head CT, and EKG were unremarkable. Patient remained febrile for approximately 3 h with maximum temperature 38.9 °C. She later became alert and oriented to person, place, and time; however, she remained drowsy with no recollection of events. She was transferred out of the ICU on postpartum day 1 and discharged to home postpartum day 2 in stable condition.

Discussion

Fever is a known side effect of misoprostol administration; however, severe hyperthermia and altered mental status are less common side effects.

The differential diagnosis for severe hyperthermia and altered mental status in the acute postpartum period is broad. Early empiric treatment for presumed sepsis should be initiated, including aggressive fluid resuscitation, antibiotic administration within the first hour, blood and urine cultures, and routine labs [4]. Both of our patients had increased suspicion for sepsis given their leukocytosis. Origin of infection can include intra-amniotic infection, urinary tract infection (UTI), and respiratory processes. While intra-amniotic infection or endometritis can lead to sepsis, it is unusual to develop symptoms so acutely after delivery, especially in the setting of very transient hyperthermia and altered mental status. Supportive care and treatment of acute delirium and agitation are also warranted.

Neither of our patients exhibited profound hypertension.

Had either of our patients shown severely elevated blood pressures, acute treatment with anti-hypertensive agents would have been initiated. There was increased concern for eclampsia for the first case in the setting of known preeclampsia without severe features and elevated blood pressures; however, the patient's presentation would be atypical given high fever is not a common finding in eclampsia. Additional workup included a 12-lead ECG to rule out any cardiac etiology as well as brain imaging to rule out other causes of altered mental status. In both our patients, ECGs proved normal other than sinus tachycardia, likely secondary to acute fever and inflammatory response associated with the misoprostol. Brain imaging was also unremarkable.

Our cases demonstrate symptoms of hyperthermia with altered mental status can be a rare adverse effect of misoprostol administration and should also be included in the differential. Studies show dose and route of the misoprostol administration may be correlated to prevalence of hyperthermia. Dose-dependent misoprostol fever was shown in a multicent randomized pilot trial comparing oral misoprostol to intramuscular oxytocin for routine management of third stage of labor. Temperature > 38 °C was measured in 7.5% of patients in the misoprostol 600 µg group, 2% in the misoprostol 400 µg group, and 3% the oxytocin group. However, none of the women had a temperature > 40 °C [5]. Another open-label pilot study compared 600 µg against 800 µg of sublingual misoprostol. The 600 µg resulted in a 55% lower rate of high fever (> 40 °C) and reduced risk of severe shivering (relative risk (RR) 0.17) [6]. In our cases, a dose-dependent relationship can also be inferred, as both patients received a dose greater than 600 µg.

The route of misoprostol administration may be correlated to prevalence of hyperthermia. Pharmacokinetic studies for the use of misoprostol in other obstetric indications suggest that oral and sublingual routes achieve a higher maximum plasma concentration of misoprostol sooner than vaginal and rectal routes [7-9]. In the setting of vaginal deliveries, Khan and El-Rafaey measured serum concentrations of misoprostol acid at set intervals of 240 min after misoprostol 600 µg was administered either orally or rectally after delivery [10]. The group receiving an oral dose had a higher mean peak serum concentration than the rectal route group. This maximum was achieved on average at 18 min in the oral route group, and at 40.5 min in the rectal route group. Our cases correlate to the temporal relationship between route of administration and onset of peak concentration. The first case received a buccal dose and had onset of symptoms 1 h after administration, whereas our second case received a buccal dose and had onset of symptoms 2 h after administration. Thus, route of administration should be considered at time of misoprostol administration and at initial evaluation of severe hyperthermia and altered mental status.

PPH is an obstetric emergency and the most common cause is uterine atony [11]. Misoprostol is an often-used drug for immediate management given its low cost and temperature stable profile, especially in low-resource areas. Although a common side effect is fever, severe hyperthermia and altered mental status are uncommon [12, 13]. Our two cases demonstrate the importance of judicious treatment selection in the management of PPH. There are a few limitations to these cases presented. Both cases have overlapping differential diagnosis that may also explain the profound presentation of both patients, particularly infection. There is also no direct cause and effect that can be proven with the two cases. Finally, some of the evidence reviewing route of administration and pharmacokinetics are generalized from studies reviewing the use of misoprostol for additional obstetric indications, such as termination or labor induction. Nevertheless, care of severe fever leading to altered sensorium requires immediate management, including potential ICU admission. There is a need for future studies examining the route and dosage of misoprostol and the prevalence of hyperthermia and altered mental status. The feasibility of these studies is limited by the rarity of the outcome and high number of subjects required to power such a study.

When providers encounter a patient with acute hyperthermia and altered mental status, evaluation warrants a broad differential that includes utilization of misoprostol in management of uterine atony. Administration of more than 600 µg of misoprostol for management of uterine atony may increase the risk of this adverse event.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from all cases for medical chart review, reporting, and publication.

Author Contributions

All authors contributed to the care, data collection, review, and editing process of this report. Daniel S. Lee: patient care, chart review, manuscript production, editing, and submission. Jason Hirsch: patient care, literature review, manuscript editing. Liwen Xu, MD: patient care, literature review, manuscript production. Alexandra Havard, MD: patient care, manuscript editing. Michelle Tsai, MD: patient care, literature review, manuscript editing.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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