

## Watch out- severe hyperthermia with misoprostol!

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**Abstract:** Misoprostol, used for the prevention and management of post partum haemorrhage, can have adverse effects and should be monitored carefully. We discuss a 30 year old primigravida who received misoprostol for post partum haemorrhage. She developed high grade fever leading to altered sensorium and metabolic acidosis. She required intubation and intensive care and was salvaged.

**Keywords:** Misoprostol; fever; Drug-Related Side Effects and Adverse Reactions

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### I. Background

Misoprostol is a drug which is approved and commonly used in the management of postpartum haemorrhage. Its common side effect includes hyperthermia. Though naive in the most, it can rarely lead to life threatening consequences as in our case.

### II. Case presentation

A 30 year old primigravida was booked and supervised in our hospital. Her pregnancy had been uncomplicated and she was induced for prolonged pregnancy at 40 weeks 3 days. She underwent a vaginal delivery and gave birth to a healthy live born child of 3.3 kilograms. Following delivery, she had atonic postpartum hemorrhage which was managed by uterine massage and oxytocics i.e. 20 IU oxytocin intravenously, 0.25mg of methergin intramuscularly and 400 micrograms of misoprostol per rectally. She was shifted to the postpartum ward where her condition remained stable. Two hours post delivery; she was noted to have developed high grade fever (108 F) of sudden onset without chills and rigors. She had tachycardia with a pulse of 120 per minute and blood pressure of 100/70mmHg. Her sensorium deteriorated and she soon became delirious. There was no bleeding per vaginum. Uterus was well retracted and there was no abdominal distension or free fluid.

The blood gases were normal. The patient was resuscitated with oxygen and crystalloid infusion. A hemogram, serum electrolytes and septic screen were ordered. She received intravenous paracetamol 1 gram. Tepid sponging was done along with bladder and stomach washes with cold normal saline. She was started on broad spectrum antibiotics in the form of cefepime, gentamicin and meropenem. Medicine and anaesthesia consultation were sought. There was no evidence of infection in the urinary tract, chest, neurological and cardiovascular system examinations. Her haemoglobin was 12 g/dl, platelet count 80,000 per millilitre and total leucocyte count of 9000 per millilitre. Blood smears for malaria and dengue serology were negative. USG abdomen was normal and so were her electrolytes. Electrocardiogram revealed sinus tachycardia.

Her temperature got lowered to 104F in one hour. However, she became violent and developed metabolic acidosis with a pH of 7.1. She was shifted to the intensive care unit. Bicarbonate correction was administered and she was ventilated and put on ionotropes. Thereafter, she maintained her vitals and was weaned off the ionotropes and ventilator over 2 days. She was extubated on day 3 and discharged in satisfactory condition on day 6.

### III. Discussion

The body temperature of 98.6 Fahrenheit or 37 Celsius is described as normal for human body. Core body temperature above 104 Fahrenheit (40 Celsius) is defined as severe hyperthermia. While hyperthermia is a condition with raised body temperature with hypothalamic set point, in hyperpyrexia there is a rise in the body temperature without change in hypothalamic set point. The mechanisms to conserve heat and raise temperature like shivering are seen with hyperpyrexia. Hyperthermia, on the other hand is associated with an unregulated elevation of body temperature. Various drugs are known to cause elevated temperatures, the commonest of these being anticholinergics, antipsychotics, inhalational anaesthetics, succinylcholine to name a few. (1) Temperature rise with misoprostol has been postulated to be due to hyperpyrexia. (2) Drug induced hyperthermia syndromes include serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic and sympathomimetic poisoning. (3, 4)

In our patient, the initial differentials for the fever included drug induced hyperthermia, sepsis, malaria, dengue, embolism, heat stroke and pontine haemorrhage. There was no evidence of infection or sepsis in the patient before and after her admission to the hospital. Her total leucocyte count was normal and so were blood and urine cultures. Prophylactically we did administer a wide spectrum of antibiotics after onset of fever, though there was no evidence of infection found. She had a normal delivery without any analgesia and was on no other drugs like antipsychotics, SSRIs or recreational drugs. The only drugs she received during the last 2 hours were oxytocin, methergin and misoprostol for management of atonic postpartum hemorrhage. Fever is a common side effect of misoprostol, recommended in doses of 600-800mcg for management of postpartum hemorrhage. (2, 5-9) Our patient had received 400 micrograms of misoprostol per rectally. The temperature rise was documented 2 hours after the administration of the rectal dose of misoprostol, which corroborates with the pharmacokinetics of maximum serum concentration of misoprostol in the body with rectal route of administration, similar to findings of Leon et al for sublingual misoprostol. (8) Fever reported with use of misoprostol (10) is usually below 104 Fahrenheit and seldom is severe hyperthermia reported due to misoprostol. Our case was exceptional as the temperature shot up to 108 Fahrenheit, causing delirium, acidosis and hypotension requiring ventilation and ionotropic support.

Extreme temperatures adversely affect various body systems. Hyperthermia is associated with a host of systemic side effects most importantly on the liver, neurological system, kidneys, heart, adrenals, testis and bone marrow (10-12). Hyperthermia may decrease cerebral perfusion and increased metabolism leading to delirium, bizarre behaviour, seizures and even coma. Cardiovascular system changes in severe hyperthermia include hypotension and tachycardia. High output cardiac failure can result. Renal dysfunction is seen as reduced urine output due to both rhabdomyolysis and acute tubular necrosis. Hyperkalemia may be associated. Hyperthermia may also cause consumptive coagulopathy. Our patient experienced neurological and cardiovascular effects of hyperthermia. The management of hyperthermia related complications in our case necessitated use of ionotropes and ventilation, apart from management of acidosis, vigorous cooling techniques and antipyretics. In brief, side effects of misoprostol, though rare can be dangerous and women being administered misoprostol should be monitored for temperature rise in the postpartum period to avoid any major morbidity and even mortality.

#### Take home messages

Misoprostol is an effective and commonly used drug for management and prophylaxis of post partum haemorrhage. However, as in our case, the possibility of its side effect in the form of severe hyperthermia that can compromise the neurological, haematological, cardiovascular and renal functions should be kept in mind and women should be monitored for the development of high grade fever.

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