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CASE REPORT

MALIGNANT HYPERTHERMIA FOLLOWING INTRAVAGINAL PROSTAGLANDIN-MISOPROSTOL

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ABSTRACT: Malignant hyperthermia following intra vaginal prostaglandin misoprostol is rare. A patient presenting malignant hyperthermia following intra vaginal misoprostol was diagnosed by clinical presentation and routine lab test such as increased level of CPK, increased serum creatinine, metabolic and respiratory acidosis, increase serum potassium and myoglobin in urine. It is important to note that other known causes of malignant hyperthermia were not present. Patients was given iv cold saline, cold water lavage, cold sponging along with supportive care (With stoppage of misoprostol) and complete recovery within 3 days. Hence, here intra vaginal misoprostol should be considered as a triggering agent for malignant hyperthermia.
KEYWORD: Malignant hyperthermia, Intra vaginal misoprostol, Abortion.

INTRODUCTION: Misoprostol is a prostaglandin E1 synthetic analog, with uterotonic and cervix maturation effects. The clinical applications of misoprostol include medical abortion, cervix maturation, induction of labour and postpartum hemorrhage. Misoprostol may be administered orally, vaginally, sublingually or rectally. It is safe, stable at room temperature, with few side effects, affordable and economic:

- However, unsupervised use of misoprostol may lead to complications and teratogenicity.
- Fever and shivering after administration of misoprostol in known and is commonly observed adverse effect in labour rooms.
- We report a case which presented to us with malignant hyperthermia following intra vaginal misoprostol and was aggressively managed and discharged after 4-5 days.

CASE REPORT: A young lady 18yr old, recently married, came with complaints of minor vaginal bleed (After taking some abortion inducing pill). Patient was stable, her family and husband adamant on incurring abortion. Repetitive prostaglandin (Misoprostol) intra vaginally introduced at night, as per degree of cervical os opening. For the next 14hrs patient was completely asymptomatic. After 14hrs, she started complaining anxiety and fever, and also having palpitation.

On examination: PR=106/m, BP-110/70mmHg, RR=30/min, thoracoabdominal and temperature=102°F and breathing deeply. Within ½ to 1hr, she became unconscious and temperature reaches to 108°F and PR=146/min and within minutes started de cerebrating and gasping and landed into shock with respiratory failure and massive pulmonary oedema (BP & PR=Not recordable), SpO_2 not recordable on pulse oximeter.

Patient was immediately intubated and shifted to ventilator. Hyperthermia managed with cold sponging, cold stomach lavage and intravenous cold saline, along with it vasopressure support given to the patient. She remained on ventilator for next 16hrs, extubated and given supportive treatment along with prophylactic antibiotics and patient have complete recovery within 3 days. She was given only antibiotics (But no antimalarial) and provided other supportive care.

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Before preceding event, all blood routine tests were normal.

Normal total leukocyte count, Hb=13gm%, normal serum creatinine=0.86mg%, S. bil=0.78mg%, Sr Na=134meq/L, K=4.2meq/L, Urine R/M within normal limit, SGPT/SGOT within normal limit, CXR PA view within normal limit and ECG within normal limit.

Just after the Catastrophic event of Malignant Hyperthermia. We immediately sent the Blood Samples for Analysis and we got such Results:

- TLC = 30000/dl (high) with $P_{90}L_9M_1$, Platelet count = 70000/dl.
- Increase Sr. Creatinine = 1.8, MPQBC – negative, Increase Sr. bilirubin=1.9.
- ABG – Ph=7.0, HCO_3^- =8.9, PCO_2=64, PO_2=78, SpO_2=84, base excess =-6.
- Temperature =108°F, urine R/M = cold colored or dark colored urine, urine for myoglobin positive, urine protein +2, CPK total =3000/L units, Sr. Na= 146meq/l, K=6.5meq/L, Ca=5.6.
- ECG showing sinus tachycardia.
- CXR PA view was not possible immediately as patient shifted to the ventilator.
- CXR PA view after 24 hr of the event was within normal limit.

Appropriate correction given for deranged blood biochemistry and patient rapidly reverted with IV cold saline, cold stomach lavage with cold sponging and ventilatory support, got out of ventilator in next 16hrs, remained on conservative and supportive treatment for next 3 days and also given antibiotics. She discharged from hospital in 3 days and now doing well and having healthy life.

DISCUSSION: Malignant hyperthermia is inheritance as a autosomal dominant; the defect is typically located on the long arm of chromosome 19 involving the ryanodine receptor located on sarcoplasmic reticulum. RYR1 opens in response to increases in intracellular Ca^{2+} level mediated by L-type calcium channel. Thereby resulting in a drastic increase in intracellular calcium level and muscle contraction. The process of sequestering this excess calcium consumes large amount of ATP, the main cellular energy carrier and generate the excessive heat (Hyperthermia) that is the hallmark of disease. The muscle cell is damaged by depletion of ATP and possible, the high temperature and cellular constituents leak into the circulation including K. myoglobin, creatinine, and phosphate and creatinine kinase.[1]

Most common triggering agents are volatile anaesthetic gases such as halothane, sevoflurane, desflurane, isoflurane, enflurane or the depolarizing muscle relaxant suxamethonium and decamethonium. Other drugs that have been suspected of causing MH include catecholamine, phenothiazine and MAO inhibitors.

The most common side effects associated with the postpartum administration of misoprostol are shivering and pyrexia.[2] Higher rates of shivering and elevated body temperature are associated with oral and sublingual routes of administration, which achieve a higher and quicker maximum plasma concentration than vaginal or rectal administration.[3,4] In several PPH prevention and treatment studies, misoprostol has been associated with fever of above 40°C (104°F).[5,6] 15 other cases of high fever noted in the literature include five of 9198 cases reported from the largest hospital-based clinical trial on the prevention of PPH, in which a prophylactic oral dose of 600 micrograms misoprostol was used.[6] A PPH treatment trial in South Africa reported three women (Out of 114) with temperatures of above 40.0°C following 1000 micrograms misoprostol (200 micrograms

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orally+400 micrograms sublingually + 400 micrograms rectally).[7] In Pakistan, a single case of high fever (out of 29) following adjunct treatment with a sublingual dose of 600 micrograms was reported.[8] More recently, two multicenter studies testing an 800 micrograms regimen of sublingual misoprostol as first-line treatment for PPH reported a higher-than-expected rate of fever above 40°C in one of nine sites (36%), whereas much lower rates were recorded in the other eight sites, ranging from 0 to 9%.[9,10]

According to J Durocher et. al., 58 of 163 women (35.6%) treated with misoprostol experienced a fever of >40.0°C. High fevers followed a predictable pattern, often preceded by moderate/severe shivering within 20 minutes of treatment. Body temperatures peaked 1–2 hours post-treatment, and gradually declined over 3 hours.[11]

E-series prostaglandins (PGEs) are involved in the endogenous fever mechanism, and prostaglandin E2 (PGE2) in particular is acknowledged as the primary mediator of fever induction[12] through an interaction with the EP3 receptor. However, there is no evidence that prostaglandin E1 (PGE1), of which misoprostol is an analogue, acts differently from PGE2,[12,13] in fact, the biologically Active form of misoprostol, misoprostol acid, has been shown to bind to the EP3 receptor.

Considering this evidence, we theorize that in the fever cases presented, misoprostol may be mimicking endogenous PGEs in the thermoregulatory pathway by shifting the hypothalamic set point upwards and stimulating temperature elevation. Further pharmacologic studies are needed to validate this hypothesis. Importantly, these fevers were well managed by nurses with local treatment practices within the clinical competencies of delivery attendants.

As evident from case report, patient is having only exposure to intra vaginal prostaglandin misoprostol and no other drug and over the period of hours. Patient develops severe hyperthermia of 108°F along with sign of respiratory and metabolic acidosis along with renal failure and electrolyte disturbance with ECG features of sinus tachycardia with clinical feature as having hyperthermia 108°F and generalized muscular rigidity with decrebrate posturing. All the clinical feature and blood and urine biochemistry are suggestive of malignant hyperthermia and as soon as cold saline lavage, cold sponging, and iv cold saline started and patient get immediate relief from hyperthermia, supporting a diagnosis of malignant hyperthermia.

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