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Malignant Hyperthermia, Cardiac Dysrhythmia and Hypertension Crisis in Sublingual Misoprostol: Educational Policy for Adverse Drug Reaction Organization

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ABSTRACT

Pyrexia and shivering are the most popular side effects of postpartum administration of misoprostol, but other side effects of this drug are very rare. A 27-year-old pregnant female patient was admitted to Ayatollah Mousavi hospital (Zanjan, Iran), complaining about severe headache and the primary diagnosis of cerebral venous thrombosis. Treatment was successful after primary investigations and planed therapy for Cerebral Venous Thrombosis (CVT). Following the decision on terminating the pregnancy, five tablets of Sublingual misoprostol (200 mg) was used once evacuation of pregnancy remnants was done. About thirty minutes after the administration of misoprostol, onset of severe shivering and tachycardia (201/min) with high fever (about 41°C) and hypertension (182/123 mmHg) was observed. National Adverse Drug Reaction (ADR) form was completed. All of symptoms were alleviated 30 minutes after administration of Paracetamol 1gram (Intravenous infusion) followed by Metoprolol 50 mg (orally). According to the literature, we listed the various side effects of misoprostol. Even though the side effects of misoprostol are diverse and rare, the simultaneous occurrence of these side effects is not cited till date. These incidents are reported to the authorities as per ADR policy; nonetheless, no preventive measures are implemented. This necessitates medical educational policies to be taken into consideration to educate healthcare providers throughout their professional career as well as research.

Keywords Sublingual, Misoprostol, Postpartum, Cerebral Venous Thrombosis, Education, Policy

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Introduction

Misoprostol is a prostaglandin E1 analog derivative which is used to prevent stomach ulcers, start labor and to treat postpartum hemorrhage due to poor contraction of the uterus **(1)**. Also, it is used for its uterotonic characteristics, oral administration, and stability in ambient temperatures **(2)**. Misoprostol has oral, vaginal, rectal and sublingual formation **(3)**. Many studies have reported that the administration of misoprostol by the sublingual route is superior to oral and vaginal administration routs, **(4-6)**, as it is assumed that the minor side effects occur if taken sublingually. The most popular side effect of misoprostol administration to remove placental remnants after postpartum are fever and shivering, but other side effects of this drug are scarce **(4,7)**. While these incidents are reported via ADR forms, the preventive measures to promote patient safety remain unclear. Hence, medical

educational policies are required to probe the possible safety measures and fostering them. We are reporting a case of a pregnant woman with rare adverse drug reactions such as malignant hyperthermia, cardiac dysrhythmia and hypertension crisis following sublingual administration of misoprostol in postpartum ward with cerebral venous thrombosis.

Case Report

A 27-year-old pregnant female patient (G2P1L1) was admitted to Ayatollah Mousavi hospital (Zanjan, Iran) due to severe headache. Patient symptoms started with sudden onset of headache and its severity was intensified during pregnancy. Patient vital signs upon admission were: Blood Pressure =140/90 mmHg, Temperature=37.4°C, Respiratory Rate=25/min, Heart Rate=125/min.

Upon admission Magnesium sulfate (2 gr) was infused and the patient was carried to the critical care unit. Neurology consultation was performed, and neurologists suggested brain imaging using MRI and MRV. The results revealed left sigmoid venous sinus thrombosis and heparin infusion was commenced immediately (Figure 1). Once the decision was made about terminating the pregnancy, surgical approach was implemented to evacuate the pregnancy remnants. Following the procedure, to control the post-surgical hemorrhage, misoprostol (200 mg) was prescribed by gynecologist Five tablets of Sublingual misoprostol (200 mg) were used once evacuation of pregnancy remnants was done. About thirty minutes after the administration of misoprostol, tachycardia (201/min) and severe shivering with a high fever (about 41 °C) and hypertension (182/123 mmHg) were suddenly developed (Figure 2).

Then Paracetamol 1000 mg was infused, followed by oral Metoprolol 50 mg immediately beside the nursing care process (including removing the covering blankets, applying ice packs, and injection of sodium chloride 0.9%). All the mentioned symptoms alleviated after 30 minutes to 1 hour. These symptoms were considered to be related to the adverse effects of misoprostol which resolved by appropriate treatment (Figure 2). The listed complications were registered with the Iranian Adverse Drug Reaction Association with file number 33-77-8-01.

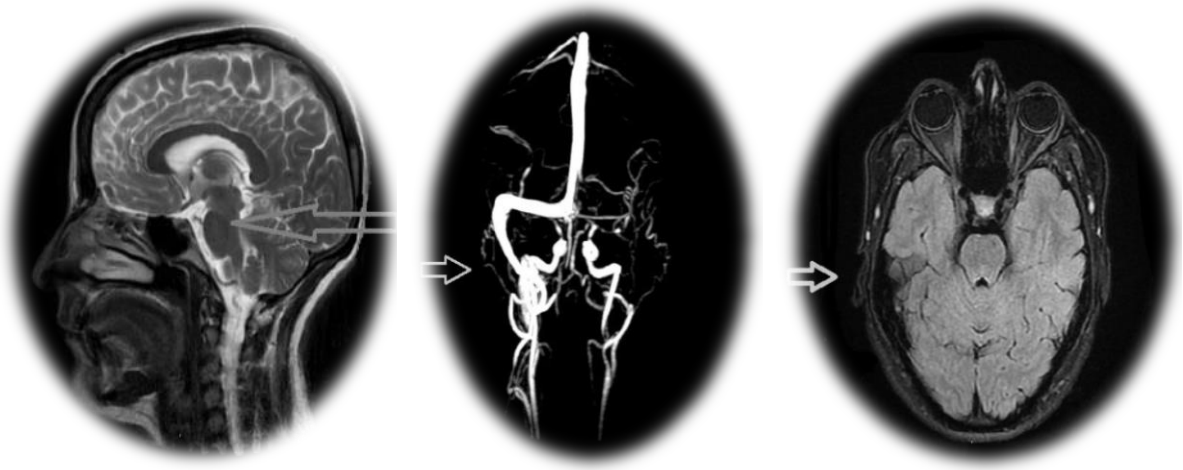
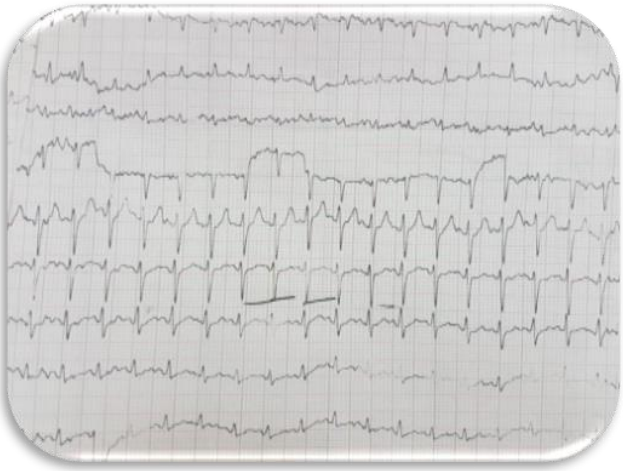


Figure 1. Left sigmoid venous sinus thrombosis in MRI and MRV



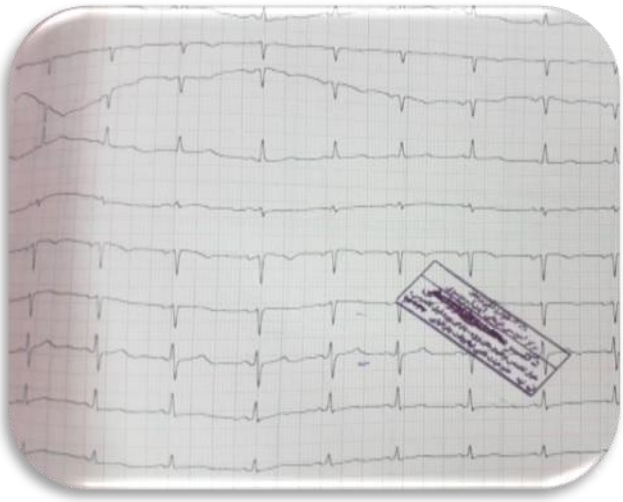


Figure 2. Electrocardiogram of a patient experiencing tachycardia following Misoprostol administration
Left: Tachycardia is evident by HR: 270 b/min
Right: Normal sinus rhythm in the same patient after controlling the symptom (HR:90/min)

Discussion

Besides the various applications of misoprostol, it is applied for the therapy of postpartum hemorrhage **(8)**. Using the correct dose is vital for safe treatment **(9)**. The most popular side effects associated with administration of misoprostol in patients experiencing postpartum hemorrhage are pyrexia and shivering **(10)**. These side effects are more popular in oral and sublingual routes of administration compared to rectal or Intravaginal routes (Table 1).

Table 1. Various routs and dosage of misoprostol

Route	Onset of action	Duration of action
Oral	8 min	About 2 h
Sublingual	11 min	About 3 h
Vaginal	20 min	About 4 h
Rectal	100 min	About 4 h

Following the oral treatment of misoprostol, it is quickly and almost totally absorbed from the gastrointestinal system **(11)**. As the result of a single dosage of 400 microgram of oral misoprostol, its plasma rate rises quickly and peaks in approximately 30 minutes **(12)**. Due to the high concentration of plasma produced in oral routes, recent studies have focused on its sublingual routes for abortion. This medication is observed to be soluble, which can be dissolved in 20 min when it is administered via sublingual membrane. It is also discovered that sublingual misoprostol has the quickest and highest peak time concentration beside the greatest bioavailability compared to the other routes **(13)**.

This report also compared this case with other case reports in the literature from 1990 to 2021. Data sources were PubMed, Embase, Google Scholar, DOAJ, Medline, Web of Science, Psych Info and CINAHL without language restriction (Table 2). Search strategy was:

((Postpartum OR Puerperium OR Pregnan* OR Gravid* OR Labor OR Obstetric) AND (Misoprostol OR Novo-Misoprostol OR Novo Misoprostol OR SC-29 OR SC-30 OR Cytotec) AND (Complication OR side effects OR adverse effects)).

In this review, 600 articles were found, of which 150 remained during the review of the title and summary. Finally, by carefully studying the text by the authors, 33 articles in the form of case reports had expressed the Side effects of misoprostol.

The peak concentration is obtained about 30 minutes after sublingual and oral treatment, compared to vaginal with almost 75 minutes. Consequently, it seems that sublingual and oral routes have the same onset of action **(14)**. This is due to the fast absorption of sublingual mucosa and evading from the first pass metabolism. (15). In studies on misoprostol to prevent postpartum hemorrhage, shivering has been reported in 32-57% of patients receiving misoprostol **(10)**. Hyperpyrexia of greater than 40 °C has been stated in various patients following 600 micrograms; and hyperpyrexia accompanied by delirium has been stated following 800 micrograms orally **(14-19)**. Although the side effects of misoprostol are

numerous and rare (Table 2), the simultaneous occurrence of these side effects is not cited till date. The primary interesting point regarding our case is the simultaneous occurrence of multiple side effects. Additionally, another highlighting point is the occurrence of cardiac dysrhythmia as a new side effect in this patient which had not been reported at the time of this report. Majority of such reports, which are recorded in ADR organizations, are crucial for various reasons. Firstly, utilizing continuous professional development of educational policies, clinicians can be well prepared to treat these situations appropriately to save lives. Also, ADR organization can reflect these reports to pharmaceutical companies to improvise the products. Besides, having set the appropriate educational policies, these reports could be included in medical school curriculum as clinical case-report-based education **(20)**.

Despite the versatility of such reports, there has been no reports available regarding the possible consequent actions among these reports. This can be considered a huge gap in health and safety regulations as well as educational and research policies. There is no point in keeping the records unless they are utilized in promoting patient health and safety via precise and concise educational timetable and content. Hence, medical education regulators and public health authorities are recommended to take ADR reports into account. Also, further studies are required to investigate various aspects of including case-report learning in medical education modules **(21)**.

As mentioned, the side effects of these medications are classified as serious ones. To prevent them, two approaches are suggested in order to be aware of the side effects of medications. First, the skills of health care workers regarding pharmaceutical matters should be improved in continuous education programs. Training content can include, but not limited to, prescribing, type of medication, side effect monitoring, and professional training updates **(22)**. The second approach is to pay attention to a person's professional identity as a guardian of the patient's health **(23)**. By including this section in the curriculum of medical students, this platform can be created so that students first get to know the dangers of these drugs, and then write prescriptions for the patient with more attention.

Conclusion

DMalignant hyperthermia, cardiac dysrhythmia, and hypertension crisis are rare side effects of misoprostol 500 µg administration. Early diagnosis and treatment of adverse drug reactions are crucial in the prevention of severe complications. Due to the importance of preventing such adverse reactions, it is suggested that authorities share the retrieved ADR data with medical schools, clinics, and continuous professional development institutions with the aim of adjusting educational curriculum. These modifications can initially make clinicians, nurses, and pharmacists familiar with uncommon adverse reactions to sublingual administration of misoprostol. Besides, pharmaceutical companies can also improvise their products based on the ADR reports. Correspondingly, utilizing reports-based learning as a part of medical education curriculum, students can benefit from a practical clinical learning.

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We thank this patient and her family for allowing us to report side effects. We also thank the administrative and radiology unit of Ayatollah Mousavi Hospital in Zanjan for providing us with the patient documents.

Conflict of Interest

Nothing to declare.

Ethical Consideration

The patient has given written consent to report drug side effects without her name and surname. The listed complications were registered with the Iranian Adverse Drug Reaction Association with file number 33-77-8-01.

Table 2. Was shown that the case reports of misoprostol Side effects

Author/References	Age	week	Dosage (mcg)	Appearance of the side effect	Route	Side effects	Treatment	Outcome
Nayki **(24)**	23	26	200	3 h	Intravaginally	First: vaginal bleeding and severe contractions, Then: Uterine rupture	Emergency laparotomy and the uterus was repaired	Recovery
Kim **(25)**	30	6.3	400	an hour later	Orally	Abdominal pain, Blood pressure: 70/40 mmHg, rupture of 1.5 cm at the left side of the uterine	The gestational sac was removed and hemoperitoneum collection was drained.	Recovery
Akhan **(26)**	27	10 weeks and 5 days	800 + 600	N	Intravaginal + Orally	intrapartum rupture of an intact uterus	laparotomy and the uterus were repaired	Recovery
Belmajdoub **(27)**	29	31	100	6h after the 4th dose	Vaginally	Severe oligohydramnios, Uterine rupture, Uterine contractions, Rupture of the water pocket	Extraction of the fetus and placenta, + conservative treatment of the uterus	Recovery
Mazhar **(28)**	38	6 weeks 4 days	1200	45min after the 2th dose	Vaginally	Acute Coronary Syndrome	O2 Plavix Nitrocontin Morphine	Recovery
Tolefac **(29)**	30	40	600	45min	Orally	Shivering and hyperpyrexia	Paracetamol and cooling.	Recovery
Matthesen **(30)**	41	-	600	-	Vaginally	Vasospastic angina pectoris cardiac arrest	CPR+ IV TNG	Resuscitated
Sharma **(31)**	21	39	600	an hour	Orally	Headache, vomiting and convulsions	Phenytoin infusion 600 mg	Recovery
Rouz **(32)**	27	9	N	Seven hours	Orally	Rupture of the cesarean section scar	Subtotal hysterectomy	Recovery
Egbe **(33)**	25	19	N	N	N	Hypovolemic shock (BP = 70/40 mmHg)	Complete hysterectomy - transfusion of blood.	Recovery
Kiran **(34)**	56	For histrectomy	400	10 minutes	Sublingual	Lack of awareness	Intubation	Recovery
Kaiser **(35)**	21	37.5	800	30 minutes	Rectal	Hyperthermia (41.5°C =106.7°F), Tachycardia (170 bpm), Transitory encephalopathy.	- Cooling protocol -Antibiotics therapy	Recovery
Nunes **(36)**	N	eighth	N	first day of the child's life	N	Moebius syndrome, Congenital central alveolar hypoventilation in child	Mechanical ventilation	Recovery
Khabbaz **(37)**	N	29	N	following day	Orally	Rupture of an unscarred uterus	laparotomy and the uterus was repaired	Recovery
Torriente **(38)**	27	10 weeks and 5 days	800 + 600	A day	Vaginally + Orally	Uterine rupture in the lower segment	Partial laparotomy Antibiotics	Recovery
Sánchez **(39)**	N	the first trimester	600+900	first day of the child's life	Vaginal Oral	Moebius Syndrome, severe malformations in the infant	Supportive care	Recovery

Berghahn **(40)**	23	23 weeks	400+400	A day	Vaginal Oral	Uterine rupture	laparotomy	Fetal Death
Hofmeyr **(41)**	N	N	N	N	N	Limb reduction anomaly	N	Teratogenic effects
Sahraei **(42)**	33	6 weeks	400	A day	Vaginal	Erythema Multiforme	Supportive care	Recovery
Pirmez **(43)**	After birth in a 10-month-old child		N	N	Oral	Moebius syndrome and holoprosencephaly	Referred for counseling	Teratogenic effects
Bennett **(44)**	34	39 weeks	75	following day	Vaginal	Rupture of the left posterior uterine wall	laparotomy	Recovery
Henderso(45)	N	term	N	N	N	Uterine rupture	laparotomy	Recovery
Bond **(46)**	19	31 weeks	30*200	2 hours	Orally	Hyperthermia, Rhabdomyolysis, Hypoxemia, Respiratory alkalosis, Metabolic acidosis	Supportive care	Fetal Death
Fossaluzza **(47)**	2 5	No pregnant	200	One month	Orally	Incontinence	Urologic investigations	Recovery
Abbas **(48)**	35	13 weeks	400	acute onset	Orally	Severe lower abdominal pain, Rupture of a scarred uterus	laparotomy	Fetal Death
Stitely **(49)**	30	13 weeks	N	N	Vaginal	Uterine scar dehiscence	laparoscopic repair	Recovery
Pallavee **(50)**	26	G2P1L1	400	N	Orally	Proximal femoral focal deficiency with fibular hemimelia syndrome, Ectopic left kidney	Orthopedic investigations	Teratogenic effects
Béné **(51)**	17	9 weeks	400	1 h	Orally	Diarrhea, Abdominal pain, Acute respiratory distress, Anaphylactic shock	Adrenaline+ betamethasone+ methylprednisolone+ dexchlorpheniramine	Recovery
Goffman **(52)**	23	34 weeks	800	28 weeks	Orally	Moderate micrognathia- condensed proximal long ossein's of both top,Lower limbs- two-sided fifth finger clinodactyly and two-sided secondary toe clinodactyly, Hemivertebra at T10 level- Missing pubic ossein, Two-sided lost knee ossification cores, Hypertelorism, Open large flattened anterior fontanelle, A broad nasal bridge	referred for counseling	Teratogenic effects
Rosa **(53)**	boy 1 year and 7 months		N	≈28 weeks	Orally	Poland syndrome	Referred for counseling	Teratogenic effects
Marchese **(54)**	After birth in a 5-month-old female		N	N	Orally	Proximal femoral focal deficiency and fibular hemimelia	Orthopedic treatment	Teratogenic effects
Franco **(55)**	40		N	N	Orally	coronary artery spasm.	Coronary Care	Recovery
Ramadan **(56)**	31		200	thirteen	Orally	Vaginal Bleeding	Total abdominal hysterectomy	Recovery

N= Not reported

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