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Case report

Coronary artery vasospasm after misoprostol treatment for incomplete abortion: a case report ☆,☆☆,★

Francisca María Muñoz-Franco [a,*], Francisco Javier Lacunza-Ruiz [a], David José Vázquez-Andrés [a], José Ramón Rodríguez-Hernández [b]

[a] Cardiology Department University Hospital Virgen de La Arrixaca, El Palmar, Murcia
[b] Gynaecology and Obstetrics Department University Hospital Virgen de La Arrixaca, El Palmar, Murcia

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ABSTRACT

Misoprostol is widely used for the medical management of incomplete abortion. Few serious adverse events have been reported, so it is considered a safe drug. We present a case of a 40-year-old woman in which misoprostol preceded coronary artery spasm.

1. Introduction

Clinical spontaneous abortion occurs in between 12% and 14% of pregnancies, and 80% occur before the 13th week of pregnancy [1]. The diagnosis can be made based on beta hCG serum trend, clinical history and ultrasound criteria, and the aim of the treatment is to evacuate the uterine cavity. Traditional surgical evacuation has been replaced by expectant management or medical treatment with prostaglandin analogues due to decreased cost, the reduction of bleeding, fewer surgical and infectious complications, and the ease of overall management of the nonsurgical approach [2,3].

Prostaglandin E2 analogues, such as sulprostone, are no longer used due to a reported association with severe cardiovascular complications attributed to coronary spasm [4]. Prostaglandin E1 analogues, such as gemeprost and misoprostol, took their place and are considered safe drugs [5,6]. In general, misoprostol is most commonly used due to the ease of administration and the molecular stability of this drug, which allows storage at room temperature. Additionally, cerebrovascular events and serious cardiovascular complications related to coronary artery spasm have been reported related to the use of gemeprost [5,7]. However, very few cases have been reported with misoprostol use. We present a case of a 40-year-old woman with a history of smoking and hypercholesterolemia who suffered a coronary artery spasm after using misoprostol.

2. Case report

A 40-year-old G6P2 women with no prior abortions and three prior miscarriages presented to the hospital reporting a last menstrual period 65 days prior and complaining of moderate to heavy vaginal bleeding and lower abdominal pain. She was an active smoker (20 cigarettes per day) and had a medical history significant for hypercholesterolemia (under dietary treatment) and migraine without aura. She reported no current medications and denied any substance abuse.

Pelvic exam showed a small amount of blood in the vagina and no other pathological findings. Serum beta hCG level was 2802 mIU/mL. Transvaginal ultrasonography showed no gestational sac and a 15-mm heterogeneous endometrium. The physician presumed a diagnosis of incomplete abortion and treated her with misoprostol 400 mcg vaginally daily for 4 days and analgesia

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* Corresponding author at: Cardiology Department, Hospital Universitario Virgen de La Arrixaca, Ctra. Madrid- Cartagena, s/n. El Palmar, 30120, Murcia, Spain. Tel.: +34 636 83 34 21; fax:+34 968 36 95 58.
E-mail address: fca.mariamf@gmail.com (F.M. Muñoz-Franco).

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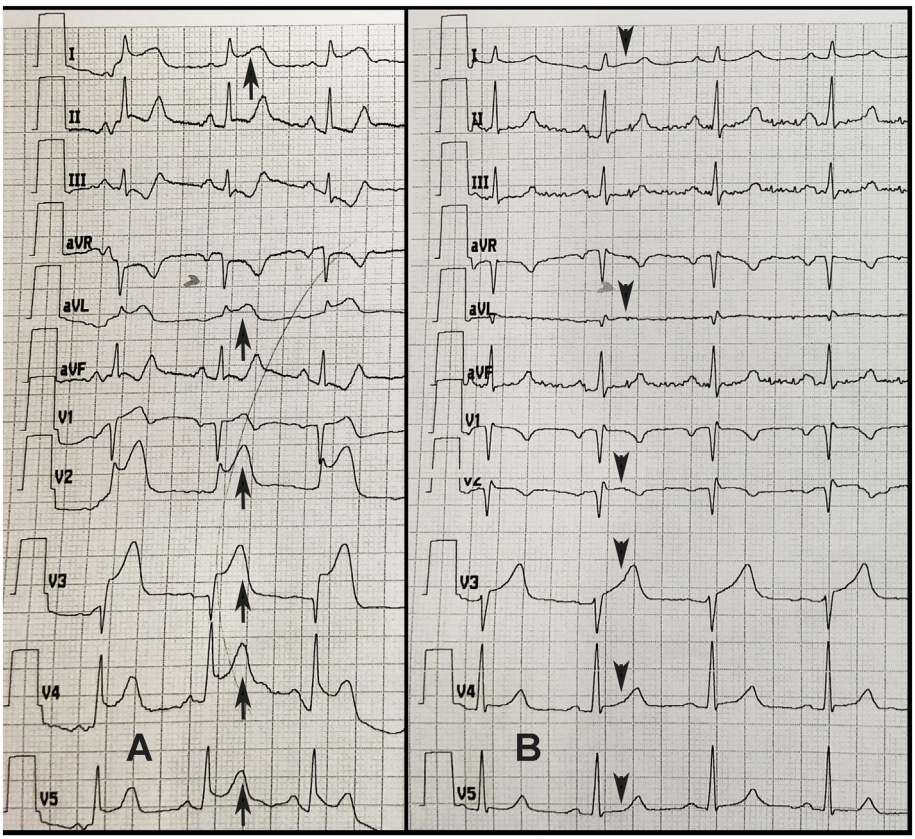

Fig. 1. EKG of a 40-year-old woman suffering crushing chest pain 20 min after the intake of misoprostol 400 mcg vaginally. (A) EKG shows ST elevation on I, aVL and V2–V5 leads (see arrows pointing up). (B) EKG shows normalization of the ST segment (see arrows pointing down) after the administration of nitrates (nitroglycerin 50 mg in intravenous infusion).

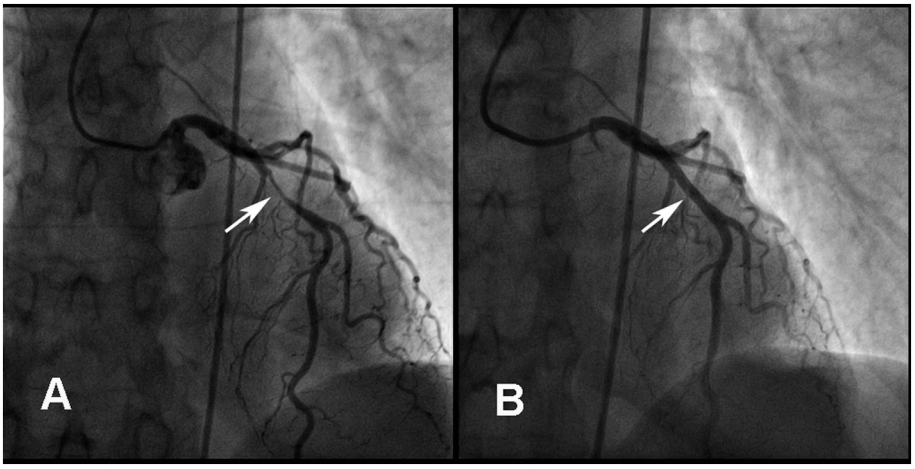

Fig. 2. Coronary angiography of a 40-year-old woman referred for a crushing chest pain and EKG changes after the intake of misoprostol 400 mcg vaginally. (A) Figure shows a very tight lesion in middle LAD (white arrow) with an important vasospasm of the vessel. (B) Figure shows the result after nitroglycerin intracoronary infusion and stent deployment in the lesion (white arrow).

alternating ibuprofen 400 mg orally and acetaminophen 500 mg orally if needed.

Twenty-four hours later, the patient presented again to the emergency room complaining of crushing chest pain radiating to her left arm, nausea, vomiting and dyspnea. She denied previous similar episodes. These symptoms began suddenly 20 min after the first intravaginal administration of misoprostol. The patient continued to deny use of any other medication or illicit drugs, so no toxicology screen was performed. The patient appeared diaphoretic and pale, and had an initial blood pressure of 123/49 mmHg, heart rate of 66 beats/min, oxygen saturation of 100% without additional oxygen supply and no fever. The presence of vaginal bleeding was not reported. Electrocardiogram (EKG) showed sinus rhythm (70 beats/min), narrow QRS and an ST-segment elevation on leads I, aVL and V2 to V5 (Fig. 1A). The physicians diagnosed acute coronary syndrome and administered acetylsalicylic acid 300 mg orally, clopidogrel 600 mg orally and nitroglycerin 50 mg in intravenous infusion, normalizing the ST-segment elevation

(Fig. 1B) a few minutes after the beginning of this therapy, thus suggesting a vasospastic component of the lesion. She was transferred to a reference hospital for primary angioplasty.

Coronary angiography demonstrated a severe stenosis in the middle segment of the left anterior descending artery (LAD) (Fig. 2A), which was recovered completely after the administration of intracoronary nitroglycerin, showing an atherosclerotic plaque with only mild stenosis, all of these compatible with coronary spasm. A direct drug-eluting stent was implanted in the lesion to avoid new recurrences, with good angiographic results. The patient returned to the intensive care unit where she recovered without complications.

3. Comment

Misoprostol is a prostaglandin E1 semisynthetic analogue widely used in obstetric and gynecology practice because it increases the frequency and intensity of uterine contractions, produces cervical ripening, dilation and softening of the cervix. In addition, it acts as a vasomotor and bronchodilator agent [8]. The most common adverse effects of misoprostol are gastrointestinal, whereas cardiovascular effects are hardly known [9]. We accessed ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?term=misoprostol&Search=Apply&recrs=e&age_v= [accessed 13 may 2019]) to review all completed studies related to misoprostol use in adults (n=248), most of which were related to prevention of peptic ulcer or gynecological use. We found no adverse cardiovascular effects reported. However, the French Regional Pharmacovigilance Centre [10] reported 63 cases of cardiovascular effects related to misoprostol, seven of them being angina, identifying some cardiovascular risk factors related to these adverse effects, such as age >35 years, smokers or high doses of vaginal misoprostol.

The effects of prostaglandin E2 (PGE2) on vascular tone are poorly known. The E prostanoid (EP) receptor subtypes activated by PGE2 are involved in the control of vascular smooth muscle tone. EP1 and EP3 are involved in the vasoconstriction induced by PGE2, whereas the activation of EP2 and EP4 causes vasodilatation. Unlike other PGE2 analogues that activate the four prostaglandin receptors, misoprostol stimulates EP2, EP3 and EP4 receptors but not EP1 receptor, so it is expected to have fewer adverse actions. However, its high affinity to the EP3 receptor would justify that the misoprostol has a vasoconstrictor effect [11,12]. According to previous studies in animal models, misoprostol, as an agonist of constrictor EP3 receptors, induces vasoconstriction, with decreased perfusion of the cortex and medulla, with both renal artery and medullary interstitial infusion [13]. Additionally, administration of misoprostol (EP3/EP2 agonist) also elevates plasma noradrenalin levels in a dose-dependent manner. Noradrenalin is a potent endogenous vasoconstrictor, and misoprostol elevates its plasma levels more than sulprostone [14].

Although we cannot prove a direct effect of misoprostol on the spasm of the patient, there are previous studies [9–11] that support the vascular effects of the drug. Besides, the intake of misoprostol and the apparition of the cardiac event are very closely related in time, and there is not an alternative cause explaining the symptoms of the patient, all of them strongly suggesting a drug effect on the patient vascular tone. According to the WHO-UMC scale and the Naranjo scale, both evaluating the hazard of causality of an adverse drug reaction, the reaction would be very probably related to the drug [15,16].

Regarding the presence of an underlying lesion, this fact does not preclude the spasm. Coronary spasm may appear both on healthy vessels as well as on diseased segments [17–19]. Coronary spasm could be related to an individual predisposition in which many factors may be contributing, such as autonomic nervous system, endothelial dysfunction, oxidative stress, genetic factors or low-grade inflammation [20]. The characteristic that defines spasm is the restoring of original vessel size after the administration of a vasodilator, and that was seen in the angiography of this patient. In fact, this is the main contribution of our case, the clinical evidence of coronary spasm soon after drug administration, demonstrated by angiography.

Regarding the treatment, we cannot evaluate the appropriateness of this point. It is well known that misoprostol is one of the most common treatments in patients with incomplete abortion and some other clinical conditions such as persistence of embryonic remains or heavy bleeding. The latter was the reason why she received the drug. However, the dose of misoprostol administered did not fit the recent recommendations of WHO [21]. Nevertheless, we believe that this issue does not invalidate the findings that we had.

In conclusion, although very uncommon, the use of misoprostol may induce coronary artery spasm. It seems not to be related to the dose usually recommended in gynecology. Instead, this could reflect an individual predisposition to the EP3 effects of the drug on some individuals.

This case illustrates this issue, providing objective data of coronary spasm, and encourages us to be cautious with this treatment, especially in those patients with higher risk of cardiovascular complications such as smokers, diabetics, aged over 35 years and obese [10]. As a final recommendation, we would suggest cardiovascular risk assessment before the administration of misoprostol and close monitoring of the patient during the first hours after the administration of the drug, especially in patients with cardiovascular risk factors.

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