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Raynaud's phenomenon of the nipple as a side-effect of labetalol: Case report and literature review

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ABSTRACT

Raynaud's phenomenon of the nipple is an unusual side-effect of labetalol use. There is one official report from the United Kingdom. The present case concerns a 30-year-old woman, gravida 1, para 0, who developed pre-eclampsia and was treated with labetalol but subsequently reported neuropathic pain of the nipple. Nifedipine was then started as part of her treatment plan for blood pressure control and she no longer reported pain, despite being given six more doses of labetalol. Nifedipine is the first-line of treatment for Raynaud's phenomenon. The concomitant use of labetalol with nifedipine by a woman with Raynaud's phenomenon of the nipple has not been discussed before. The goal of this review is to raise awareness of this drug-induced phenomenon and to add to the limited literature available on this subject.

1. Introduction

The vasospasm of the arterioles was first described by Maurice Raynaud, in his publication titled "Local asphyxia of the extremities" in 1888 [1]. Raynaud's phenomenon has since been reported many times, in both men and women. However, it seems more prevalent in women, affecting 20% of women of childbearing age [2]. Originally Raynaud described this manifestation in the extremities, such as toes and fingers, but recently it has also been reported to affect many other parts of the body, including the nipple [3].

Gunther originally reported nipple vasospasm, but it was Coates who elaborated and linked nipple vasospasm to Raynaud's phenomenon [3,4]. Vasospasm of arterioles is a normal physiological response to cold temperatures, but has also been reported to be secondary to stress, caffeine consumption and smoking. These risk factors must be avoided in patients with Raynaud's phenomenon [4,5,6]. The phenomenon is associated with a tri-phasic color change. The extremity goes from white due to ischemia, then blue from the deoxygenation and finally red upon reperfusion. This process is often associated with pain, burning and paresthesia (neuropathic pain).

Labetalol has been reported to be a cause of Raynaud's phenomenon of the nipple [7]. However, this association is rare, and the incidence unknown. We present a case in a pregnant woman with pre-eclampsia describing a burning sensation in her nipples after being administered labetalol, which resolved after nifedipine administration. To our knowledge this is the first case report to describe this progression of events. Drug-induced Raynaud's phenomenon appears to be an under-recognized medical concern and is not mentioned often in the literature. It is important to raise awareness in the healthcare community, as it is a preventable and treatable cause of neuropathic nipple pain.

2. Case Report

The case concerns a 30-year-old white woman, gravida 1, para 0, with no significant medical history. Her antenatal care was uncomplicated until week 32, when she was diagnosed with gestational hypertension during a regular follow-up visit and she was started on nifedipine XL 30 mg once daily. At week 34, the patient continued to have elevated blood pressure and consequently her nifedipine XL was increased to 60 mg daily. The next day, in addition to continued hypertension despite medical management, the patient complained of a headache, and a urine analysis revealed a protein:creatinine ratio of 0.56 (normal <0.20). The decision was made by her doctor to send the patient to her local rural hospital for evaluation of pre-eclampsia. At the hospital, the patient's blood pressure was elevated at 168/69 mmHg, so the decision was made to treat the patient with intravenous labetalol 100 mg, betamethasone, intravenous penicillin, and magnesium sulfate. The decision was made to transfer the patient to a tertiary hospital equipped to manage high-risk pregnancies.

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After transfer, her blood pressure was at the upper limit of normal. The patient reported no symptoms indicative of severe pre-eclampsia, such as headache, vision changes or pain in the right upper quadrant. The decision was made to discontinue the nifedipine XL 60 mg, which was believed to be masking the high blood pressure associated with pre-eclampsia. Three days after discontinuing nifedipine, the patient had severe hypertension, for which she was again given intravenous labetalol, initially 20 mg, followed by an additional 40 mg. With each administration of labetalol, she complained of intense areolar burning. Upon further questioning, she reported that she had experienced the same burning sensation after the administration of labetalol in the outlying facility. Additionally, further history was obtained indicating a similar sensation of areolar burning felt by the patient in prior years when she had been out in cold winter weather. The patient had never noticed any color change, although she had not examined her breasts during these events. The present areolar burning lasted 15–20 min and began about 20 min after labetalol administration. It was initially intense, then slowly decreased until it completely resolved about one hour after administration. Approximately one hour after resolution of the nipple pain, the patient was administered 10 mg of nifedipine for breakthrough hypertension. At this time, the decision was made to give the patient scheduled daily nifedipine XL for constant blood pressure control, with intravenous labetalol and nifedipine for breakthrough elevated blood pressure. After beginning the scheduled nifedipine XL, no further areolar pain was noted, even after six further doses of labetalol. The patient eventually underwent an uncomplicated cesarean section secondary to failed induction of labor, with the birth of a healthy boy. No additional symptoms were described.

3. Literature Search

We conducted a PubMed search using the words “Raynaud's phenomenon of the nipple” without a publication date parameter. This yielded 25 items, of which only one case study directly discussed Raynaud's phenomenon of the nipple induced by labetalol. Through the citations of that case study we were able to find another relevant article, from the Netherlands, which reported three other cases.

4. Discussion

Drug-induced Raynaud's phenomenon of the extremities has been reported multiple times [8–10]. The medications that are associated with this neuropathic pain are cancer chemotherapy drugs like cisplatin and bleomycin, β-adrenoceptor blockers and most recently tyrosine kinase inhibitors [8,9]. Despite the many reports of drug-induced Raynaud's of the extremities, as noted above there are few reports of drug-induced Raynaud's of the nipple. To our knowledge this is the first case reported from the United States to document an association between Raynaud's phenomenon of the nipple and labetalol use, with subsequent disappearance of the pain after nifedipine administration. Only four other cases worldwide have been reported of nipple pain after labetalol administration [7,10]. Three cases of pregnant women who experienced nipple pain after use of labetalol were reported to the Netherlands Pharmacovigilance Centre, which maintains that country's voluntary adverse drug reaction reporting system [10]. Interestingly, in the three cases reported, the onset of nipple discomfort coincided with the maximum plasma concentration of labetalol, which is reached within 30–60 min [11]. In addition to these cases, there has been one official case report, from the United Kingdom, of nipple pain experienced by a pregnant female after labetalol use [7]. The nipple pain was thought to be a manifestation of Raynaud's phenomenon and not just a coincidental side-effect of labetalol [7]. Thus, the only reports in the literature of labetalol being associated with Raynaud's phenomenon of the nipple all involved pregnant women [7,10].

Labetalol is a dual α_1 and β_1/β_2-adrenergic receptor blocker. The efficacy and safety profile of labetalol are favorable and the drug is commonly used in pregnancy because, unlike purely β blockers, combined α and β drugs are less likely to decrease uteroplacental blood flow. Labetalol is often the first-line treatment for gestational hypertension. Gestational hypertension needs to be monitored closely, given that it can progress to pre-eclampsia and eclampsia, as in the case of the patient presented in this case report. Given all we know about labetalol, the exact mechanism of how it causes Raynaud's phenomenon (of the nipple or extremities) is not known. In a randomized double-blind crossover design study by Steiner et al. [12] propranolol and labetalol did not trigger Raynaud's phenomenon of the hands in patients with primary Raynaud's. Although that study did not have a large sample, it did highlight the fact that many variables are in play and that drug-induced Raynaud's phenomenon is multifactorial.

Nifedipine has been known to alleviate the symptoms of Raynaud's phenomenon of the nipple [13]. Nifedipine is a calcium-channel blocker that inhibits the uptake of calcium by vascular smooth muscle cells, resulting in a vasodilatory effect. Due to this mechanism of action nifedipine is used to treat both hypertension and Raynaud's phenomenon. In the present case, the burning sensation disappeared completely after administration of nifedipine, despite the fact that six additional doses of intravenous labetalol were administered. It is presumed that the vasoconstriction caused by labetalol was countered by the vasodilatory effect of nifedipine, and as a consequence the pain subsided. Tri-color change is a common feature of Raynaud's phenomenon but it was not reported by the patient. However, she did not look at her breasts and therefore color change might have been present but not noted.

A study conducted in 2012 found that intravenous labetalol and nifedipine were equally effective in controlling severe hypertension in pregnancy [14]. Nifedipine can therefore serve as an alternative antihypertensive medication for pregnant women who report nipple discomfort and in whom Raynaud's phenomenon is suspected. Health professionals should be aware of drug-induced Raynaud's phenomenon of the nipple, so that it is not mistaken for other medical causes of nipple pain, such as *Candida albicans* infection or mastitis, due to its similar clinical presentation [13,15–18]. In an article by Anderson et al., out of 12 patients with Raynaud's phenomenon of the nipple, eight received antifungal therapy unnecessarily prior to being diagnosed with Raynaud's [16]. Furthermore, drug-induced Raynaud's phenomenon of the nipple could negatively impact breastfeeding. It has been well established in the literature that Raynaud's phenomenon of the nipple can be experienced by many mothers as a result of breastfeeding [13]. The pain is often so severe that it causes some to stop breastfeeding. Thankfully, Raynaud's phenomenon of the nipple due to breastfeeding without other causes has been shown to respond to nifedipine and enable women to continue breastfeeding [13,16]. The American Academy of Pediatrics has endorsed the use of nifedipine in breastfeeding mothers for its safety profile, given that <10% of the medication is transferred to the breast milk [19].

The goal of this report is to raise awareness of this drug-induced phenomenon and add to the limited literature available on this subject by summarizing the pertinent articles and presenting a new case. Since Raynaud's phenomenon is a preventable and treatable cause of nipple pain, it is important to raise the awareness of pediatricians, lactation consultants and also physicians so that they are aware and can better avoid and manage the manifestations. More importantly, however, healthcare professionals should ask the patient about nipple discomfort after they have started taking labetalol. Many patients will not volunteer that information, due to embarrassment or for various other reasons. If labetalol-induced Raynaud's phenomenon of the nipple is diagnosed early in the treatment of gestational hypertension, healthcare professionals can avoid not only the discomfort experienced by the patient but also unnecessary treatment for infections like *Candida albicans*, and potentially avoid interruptions in the breastfeeding regimen of the mother.

Contributors

Jesus Avila Vega contributed to study concept and design, acquisition and interpretation of data, drafting and revising the manuscript.

Enrique Urrea-Mendoza contributed to study concept and design, acquisition and interpretation of data, drafting and revising the manuscript.

Christy Lee contributed to revising the manuscript.

All authors saw and approved the final version.

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This case report was peer reviewed.

Declaration of Competing Interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

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