

Synthetic hormone, drospirenone, triggered severe venous thromboembolism: a case report

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WRITER'S COMMENT: As a Global Disease Biology major in the College of Agriculture and Environmental Sciences, I am very rarely presented with opportunities to write formal reports centered around a single patient. So when Professor Herring introduced our most daunting writing assignment as a true, and formal, medical case report, I was ecstatic. Both fortunately and unfortunately, I had the perfect subject. In 2007, my mother was initially misdiagnosed with an acute case of bronchitis, only to later discover her true diagnosis of severe venous thromboembolism due to combined oral contraceptives. As an eight-year-old child, I was never able to grasp the severity of her condition. This writing assignment allowed me to further investigate my mother's experience and diagnosis, in a way that my eight-year-old self could never have understood. By hearing her memories and reading through her past medical documents, I collected both the subjective and objective information I needed to not only write this piece, but to finally understand and come to terms with her diagnosis.

INSTRUCTOR'S COMMENT: In my Writing in the Professions: Health course, one assignment is a formal case report. The students find someone who is sick or hurt and write a detailed and technical account of the problem. I like to ask them to stretch, and write the paper so that it reads like a real professional case report. It is a daunting task, surely the most difficult assignment in any of my classes. The students have not yet been to medical school, yet must write as if they are expert epidemiologists with the CDC. The language, for instance, must be relentlessly technical. It's not itching, it's "pruritus;" it's not a

headache, it's "cephalalgia." Madison had her hands full merely doing what the assignment asks, but she takes it a step further. She digs in and discovers that her case involves both a misdiagnosis and a misadventure with a drug therapy. This is precisely what a professional case report would do; the goal is to identify a problem that readers need to watch out for in their own clinics and hospitals. So any physicians reading this, pay attention. You might learn something.

—Scott Herring, University Writing Program

Introduction

Drospirenone is a synthetic progestogen derived from the aldosterone blocker spironolactone. It is structurally related to progesterone and has antiandrogenic and anti-mineralocorticoid properties, resulting in the suppression of LH activity and alteration in cervical mucus and endometrium. Since about 2002, 3 mg of drospirenone has been marketed in combination with 30 mg of ethinylestradiol in combined oral contraceptives (COCs). The risk of venous thromboembolism is increased among drospirenone-containing COC users (11-12/10,000 women per year) compared with other progestin-containing COC users (3-9/10,000 women per year) (Gronich et al. 2011). Here, we report a case of initial misdiagnosis, followed by sudden severe venous thromboembolism in a patient who received drospirenone-containing COCs for six months without previous complications.

Case Presentation

A 35-year-old female aerobics instructor presented with discomfort and pressure-like sensations in the right thoracic cavity, after a six-month history of prescribed drospirenone-containing COCs to regulate her menses. The patient, with chief complaints of sudden pain in the right pleural cavity and subtle respiratory distress, was admitted to a community hospital where she was treated symptomatically for acute bronchitis. Upon admission, a PA and lateral chest x-ray demonstrated the left and right lungs were well ventilated, the cardiac silhouette remained within normal limits, and there were no indications of pneumothorax or pleural

effusions. With no acute pulmonary disease identified, the patient was incorrectly prescribed 500 mg of Amoxicillin every 12 hours before being discharged.

Five days following the misdiagnosis, the patient again presented severe pleuritic chest pain, worsening substernal chest pain, and significant shortness of breath. Due to the patient's allergy to Vicodin, morphine was administered upon admission into the ICU. A clinical examination included a spiral CT scan with PE protocol confirming the diagnosis of left upper lobe, left lower lobe, and right lower lobe pulmonary emboli. The CT scan also revealed a large total occlusion of the left main pulmonary artery extending into the branches of the left upper and left lower lobes. In addition, sizeable pulmonary emboli were seen at the right lower lobe pulmonary arteries and extending into the peripheral branches. A small right pleural effusion and a right lower lobe infiltrate, thought to be most compatible with a pulmonary infarct, were also noted. The spiral CT scan confirmed the cardiac size was within normal limits. However, a 2D echocardiogram revealed a mild enlargement of the cardiac chamber, right atrium, and right ventricle (the left atrium and left ventricle remained normal). There was otherwise no mediastinal axillary anomaly.

A CT scan of the abdomen, showing axial images acquired from the inferior aspect of the diaphragm to the pubic symphysis at 5 mm intervals with contrast, revealed an exudative right pleural effusion, right basilar atelectasis, and right lower lobe parenchymal infarct present on the lung bases. A bilateral lower extremity deep venous duplex Doppler ultrasound revealed no evidence of deep vein thrombosis to the bilateral lower extremities above the patella. The patient denied having any history of malignancies or masses, and the possibility of an underlying malignancy was considered in the differential diagnosis. Noted predisposing factors emphasized high-risk in the patient's routine use of drospirenone-containing COCs for six months prior to hospitalization, thus enhancing the probability of deep vein thrombosis and pulmonary emboli, which led to the diagnosis of venous thromboembolism. The patient declined intravenous thrombolytic therapy with t-PA, instead opting for treatment through low molecular weight intravenous heparin injections at 10,000 IU/day subcutaneously for the following six days.

On the seventh day, following completion of the heparin injections, an IVC filter (Optease) was placed in the right side of the patient's neck

from the right jugular vein access point. Following aspiration of blood, a wire was inserted traversing the jugular vein, heart, and inferior vena cava. The IVC filter was successfully inserted under fluoroscopic guidance into the infrarenal location, and the thrombus noted on the prior CT scan was no longer evident within the inferior vena cava. The patient was prescribed Lovenox and Coumadin for long term treatment of deep vein thrombosis and pulmonary emboli. Following the thinning of blood, approximately two days after insertion of the IVC filter, the patient was discharged in improved condition on 3.5 mg Coumadin daily. An eight-month follow-up appointment confirmed no abnormalities in the patient's menstruation and no recurrences of venous thromboembolism.

Discussion

Venous thromboembolism (VTE), its name derived from the combination of deep vein thrombosis and pulmonary emboli, is a multifactorial disease that typically represents the interaction of both genetic and acquired factors. In addition to drospirenone-containing COCs, underlying risk factors include obesity, smoking, recent surgery, trauma, and acute or chronic medical illnesses; these acquired factors are generally more common in the development of VTE than the genetic factor of inherited thrombophilia. Routine use of COCs has been shown to increase hemostatic parameters and therefore pose a risk of developing VTE outcomes. Due to the nature of drospirenone, observational studies examining the association between COCs and VTE are particularly sensitive to population characteristics (Madigan and Shin 2018). Factors to consider when studying the association between drospirenone-containing COCs and risk of VTE involve comparing COC users of similar profiles: matching age, economic background, first/repeat users, overall health conditions, and presence of previously acquired VTE factors (Larivée et al. 2017).

Underlying independent risk factors of VTE, such as advanced age, obesity, and history of cancer, were completely absent in the patient, leading to an initial misdiagnosis of acute bronchitis. Although the patient declined, intravenous thrombolytic therapy with t-PA can be used to treat VTE, in replacement of the heparin injections, and may have been appropriate in this setting due to the size of the embolus, mild hypertension, and some hypoxia. Since the patient did not have

any preexisting risk factors, closer emphasis on and evaluation of the patient's daily COC routine and recognition of the active ingredient, drospirenone, may have led to an earlier diagnosis of VTE. In order to avoid future misdiagnoses, doctors should not only assess the overall presence of underlying VTE risk factors, but consider the magnitude of hormonal therapies, especially in regards to drospirenone in the setting of thrombotic risk and pulmonary emboli. The ability of clinicians to articulate the absolute and relative risks of drospirenone, equally summarizing the negative along with the positive evidence regarding hormone therapy, can aid in early diagnosis and prevention of VTE in women.

Based on a 2012 safety review, the U.S. Food and Drug Administration (FDA) concluded that drospirenone-containing birth control pills may be associated with a higher risk of VTE in women than other progestin-containing pills. Among the six published FDA-reviewed epidemiologic studies evaluating the risk of VTE in drospirenone-containing COCs, four studies concluded a range from 1.5-fold increase to a 3-fold increase in greater risk of VTE in drospirenone-containing rather than levonorgestrel-containing COCs (FDA 2012). Although the FDA's review is ongoing, this particular case study confirms and underscores these observations. Six months after well tolerated and uneventful drospirenone-containing COC use, this young and otherwise healthy patient suddenly developed severe VTE.

Even in the most conservative studies, the risk of VTE in association with the routine use of drospirenone-containing COCs roughly doubles in comparison to the association of VTE with the routine use of levonorgestrel-containing COCs. To put this into perspective, the risk of developing VTE among women using other hormonal contraceptives is about 6/10,000, (0.06 percent), which makes the risk of developing VTE among women using drospirenone-containing COCs about 11/10,000 (0.11 percent). Although the relative risk of VTE in women using drospirenone-containing COCs is higher than for those using levonorgestrel-containing COCs, the overall absolute risk of VTE remains very low (Larivée et al. 2017). Generally, this level of risk is acceptable for women actively seeking COCs; however, future patients should be carefully educated in thrombosis-prevention measures, modifiable risk reduction, and symptoms of VTE before starting new COCs. This case study emphasizes the need for clinicians to be aware of, and ultimately

more attentive to, the possibility of VTE in young and healthy patients with routine use of drospirenone-containing COCs.

References

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