

Acute Onset of Severe Dilated Cardiomyopathy During Bromocriptine Therapy

Prashant Kaushik, Sundararama R Vatsavai, Venkatramana R Banda, Pramod K Sanghi, Masood Ahmad, and Richa Kaushik

OBJECTIVE: To report a case of severe dilated cardiomyopathy (DCMP) in a patient on bromocriptine therapy for a microprolactinoma.

CASE SUMMARY: A 31-year-old African American female, who had been receiving bromocriptine 5 mg orally daily for a microprolactinoma during the preceding month, developed severe DCMP. An echocardiogram showed a markedly dilated left ventricle with severe reduction in the left-ventricular ejection fraction in the absence of any other identifiable causes of DCMP such as a peripartum state, ethanol use, preceding systemic viral illness, chronic hypocalcemia, chronic hypophosphatemia, or chronic uncontrolled tachycardia. She improved substantially (both symptomatically and echocardiographically) after cessation of bromocriptine therapy and initiation of supportive treatment of congestive heart failure (CHF). She showed no recurrence of CHF at a follow-up visit 2 months after withdrawal of the supportive care. The patient was not rechallenged with bromocriptine due to the clinical/ethical gravity of this probable adverse effect.

DISCUSSION: Although cardiopulmonary adverse effects have been reported with the use of cabergoline (another dopamine agonist), to the best of our knowledge, this is the first case report of severe life-threatening DCMP associated with bromocriptine therapy. Causality assessment using the Naranjo probability scale revealed that the adverse drug event was probable.

CONCLUSIONS: Bromocriptine was probably associated with DCMP in a patient being treated for a microprolactinoma. Severe DCMP needs to be considered a potentially life-threatening but reversible adverse effect of bromocriptine therapy for microprolactinoma of the pituitary gland.

KEY WORDS: bromocriptine, congestive heart failure, dilated cardiomyopathy.

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Bromocriptine is a standard drug used to treat prolactinomas, the most common functional pituitary tumor. Approximately 35% of the pituitary tumors in females produce prolactin. Bromocriptine, being a dopamine agonist, decreases prolactin secretion and reduces the size of prolactinomas. Both effects are mediated by binding of the drug to cell-surface dopamine receptors, leading to reduction in the synthesis and secretion of prolactin and in adenoma cell size.

Dilated cardiomyopathy (DCMP) is a disease that involves the myocardium, primarily with impairment of left and/or right ventricular systolic pump function. This results in cardiac enlargement and, often, congestive heart failure (CHF). DCMP is not the result of hypertension or

congenital, valvular, coronary arterial, or pericardial abnormalities.

Some common adverse effects of bromocriptine are nausea, postural hypotension, abdominal cramps, fatigue, and light-headedness. Less common adverse effects include nasal stuffiness, depression, cardiac arrhythmias, hair loss, insomnia, paranoia, visual hallucinations, Raynaud's phenomenon, alcohol intolerance, and constipation. There is no obvious pathophysiologic link between DCMP and microprolactinoma. We report a case of apparent bromocriptine-induced DCMP in a patient being treated for microprolactinoma.

Case Report

A 31-year-old African American female presented with sudden onset of shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea for

Author information provided at the end of the text.

one day. She denied any preceding flu-like illness or contact with sick people. She had been diagnosed with a microprolactinoma one month before presentation, when she had secondary amenorrhea, headache, serum prolactin 289 ng/mL (reference range 3.3–26.7), and thyroid stimulating hormone (TSH) 1.02 μ U/mL (reference range 0.49–4.7). Magnetic resonance imaging of the brain had shown a non-enhancing mass lesion occupying the right aspect of the pituitary gland measuring around 8 mm in diameter (not invading the cavernous sinus or compressing the optic chiasm). The woman's fasting blood glucose level at that time was 81 mg/dL. She had been receiving bromocriptine 5 mg orally every day since then. She was not receiving any over-the-counter medicines or natural/herbal products.

The patient was not known to be hypertensive. She was nulliparous and had never consumed ethanol or cocaine. There was no history of diabetes mellitus or coronary artery disease in the patient or her first-degree relatives. Pertinent findings on physical examination included obesity (body mass index 31), HR 100 beats/min (regular rhythm), and BP 116/70 mm Hg. The jugular venous pressure (as measured in the right internal jugular vein above the clavicle with the patient reclining at an angle of $\sim 45^\circ$) was 10 cm. Fine rales were audible up to the fifth intercostal spaces bilaterally on auscultation over the posterior chest. A left-ventricular third heart sound was present. There was no pedal edema. She did not have clinical features to suggest acromegaly or thyrotoxicosis.

Three sets of cardiac enzymes and serial electrocardiograms ruled out acute coronary syndrome. A contrast-enhanced computed tomographic scan of the patient's thorax did not reveal any pulmonary embolus to the level of the segmental branches, but did show mild interstitial edema and small bilateral pleural effusions. An echocardiogram showed a severely dilated left ventricle (end-diastolic dimension 6.8 cm); no left ventricular hypertrophy; left ventricular ejection fraction 20–25%, severe global left ventricular hypokinesis with color M-mode diastolic parameters consistent with diastolic dysfunction; normal right ventricular size and function; an estimated systolic right ventricular pressure of 23–28 mm Hg; normal mitral, tricuspid, aortic, and pulmonary valves; trace tricuspid regurgitation (peak velocity of tricuspid regurgitation jet 2.1 m/sec); mildly dilated left atrium (3.8 cm); normal right atrium with a Eustachian valve; and a small pericardial effusion. There was no prior echocardiogram available for comparison, as the patient had no past history of cardiac problems.

A diagnosis of DCMP with severe CHF was made. The patient was treated with a low-sodium (2 g salt per day) diet, fluid restriction (1.5 L/day), furosemide (40 mg intravenously twice daily with potassium chloride 40 mEq orally twice daily), an angiotensin converting-enzyme inhibitor (quinapril 10 mg orally daily), and metoprolol (sustained-release preparation 25 mg orally daily). Bromocriptine therapy was discontinued.

The patient's symptoms improved to New York Heart Association (NYHA) functional class II over the next 2 days. A coronary arteriogram revealed normal coronary arteries. Her basal serum cortisol, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, insulin-like growth factor-1, and human growth hormone levels were all within normal range. Serum Cocksackie A (serotype 9) and Cocksackie B immunoglobulin M antibody titers were $<1:8$ at the time of admission, and there was no increase in the titers 4 weeks later. Furosemide, quinapril, and metoprolol were discontinued after 15 days. The patient returned to NYHA Class I 4 weeks after bromocriptine was stopped, and the LV ejection fraction improved to 65%. There was no clinical evidence to suggest CHF at a 2-month follow-up. She is being followed every month by an endocrinologist for the microprolactinoma. Since she does not want to become pregnant in the near future, estrogen and progesterone replacement is being considered.

Discussion

This case has several unique features. There was an acute onset of CHF with a severely dilated left ventricle in the absence of any well-documented causes of DCMP (eg, peripartum state, ethanol use, preceding systemic viral illness, chronic hypocalcemia, chronic hypophosphatemia, chronic uncontrolled tachycardia). The patient had a microprolactinoma and was receiving bromocriptine for one

month. There was no clinical or biochemical evidence of coexisting acromegaly or thyrotoxicosis. Significant improvement occurred in her symptoms and cardiac function after cessation of bromocriptine therapy with supportive treatment, which was successfully withdrawn after 15 days without recurrence of CHF.

Dopamine has been used for more than 35 years for treatment of CHF. Bromocriptine is a dopamine receptor agonist (acts on DA₂ receptors) and may improve hemodynamics in patients with chronic CHF.¹ CHF, constrictive pericarditis, and severe pleuropulmonary inflammatory-fibrotic syndrome have been reported with cabergoline (another dopamine agonist used in the treatment of Parkinson's disease as well as prolactinomas) therapy.² Although constrictive pericarditis has been reported with bromocriptine therapy,³ To the best of our knowledge, no case reports of severe, reversible DCMP with bromocriptine therapy are available in the literature.

Severe CHF has been very well reported with acromegaly (this is potentially reversible after treatment with octreotide and trans-sphenoidal resection of the tumor) as well as TSH-secreting pituitary adenoma.^{4,5} However, our patient did not have any of these conditions.

Patients with acute DCMP presenting early in the viremic stage of myocarditis, as suggested by fever and other constitutional symptoms, may achieve benefit from immune globulin therapy, in part because of its antiviral activity.⁶ However, our patient had no preceding or concurrent systemic constitutional symptoms or clinico-laboratory evidence of viral myocarditis.

Use of the Naranjo probability scale indicated a probable relationship between the onset of severe dilated cardiomyopathy and bromocriptine therapy in our patient.⁷

Summary

Although constrictive pericarditis with bromocriptine use and cardiopulmonary adverse effects of cabergoline have been reported in the literature, to the best of our knowledge, this is the first case report of a severe life-threatening DCMP after initiation of bromocriptine therapy for a microprolactinoma. Although the condition was reversed after stopping the bromocriptine therapy, the drug should be used with caution for this condition, keeping this potential adverse effect in mind.

Prashant Kaushik MD, Staff Physician, Department of Internal Medicine, Hospital Medicine Group, Baton Rouge General Hospital, Baton Rouge, LA

Sundarama R Vatsavai MD, Staff Physician, Department of Internal Medicine, Hospital Medicine Group, Baton Rouge General Hospital

Venkatramana R Banda MD, Staff Physician, Department of Internal Medicine, Hospital Medicine Group, Baton Rouge General Hospital

Pramod K Sanghi MD, Clinical Fellow, Division of Cardiology, Department of Internal Medicine, The University of Texas Medical Branch at Galveston, Galveston, TX

Masood Ahmad MD, Professor, Division of Cardiology, Department of Internal Medicine, The University of Texas Medical Branch at Galveston

Richa Kaushik MD, Clinical-Associate to the Hospital Medicine Group, Department of Internal Medicine, Baton Rouge General Hospital

Reprints: Prashant Kaushik MD, Hospital Medicine Group, PO Box 2511, Baton Rouge, LA 70821-2511, fax 225/387-7700, kaushikprashant@hotmail.com

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EXTRACTO

OBJETIVO: Reportar un caso de cardiomiopatía dilatada severa (CMPD) en un paciente recibiendo bromocriptina para el tratamiento de un microprolactinoma.

RESUMEN DEL CASO: Una paciente de 31 años de edad de origen afro-americana que estuvo recibiendo bromocriptina (5 mg diarios por vía oral) en el último mes para el tratamiento de un microprolactinoma, desarrolló una CMPD severa (el ecocardiograma mostró una marcada dilatación del ventrículo izquierdo con reducción severa de la fracción de eyección ventricular izquierda) no atribuible a otras causas tales como el estado de parto, consumo de alcohol, enfermedad viral sistémica precedente, hipocalcemia crónica, hipofosfatemia crónica, o taquicardia incontrolada crónica. La paciente mejoró substancialmente (sintomática y ecocardiográficamente) después de suspender la terapia con bromocriptina que fue usada como soporte del tratamiento de la insuficiencia cardíaca congestiva. Desde aquel entonces, la paciente no ha mostrado recaída hasta la última visita de control 2 meses después de haberse suspendido el cuidado de soporte. La paciente no fue re-expuesta a la bromocriptina debido a la gravedad ética y clínica de este efecto adverso.

DISCUSIÓN: Aunque se han reportado efectos adversos cardiopulmonares con el uso del cabergoline (otro agonista de la dopamina), los autores indican que este es el primer caso de CMPD severa atribuida al tratamiento con bromocriptina. Una evaluación de causalidad usando la escala de probabilidad Naranjo reveló que el efecto adverso reportado estaba probablemente relacionado al medicamento.

CONCLUSIONES: En este caso reportado, la bromocriptina estuvo asociada al desarrollo de una CMPD en un paciente recibiendo este medicamento para un microprolactinoma. Cuando este efecto adverso fue identificado, la terapia con bromocriptina fue suspendida, y con cuidado de soporte, la CMPD se resolvió en unas 4 semanas. Aunque esta condición es reversible después de suspender la terapia con bromocriptina, se recomienda su uso con precaución en el tratamiento de microprolactinomas para prevenir los serios efectos adversos de este medicamento en esta condición clínica.

Encarnación C Suárez

RÉSUMÉ

OBJECTIF: Rapporter le développement d'une cardiomyopathie congestive sévère chez une patiente recevant la bromocriptine pour le traitement d'un microprolactinome.

RÉSUMÉ DU CAS: Un mois après avoir débuté la bromocriptine 5 mg par jour, une patiente de 31 ans d'origine américano-africaine développe des essoufflements soudains, une orthopnée, et une dyspnée nocturne paroxystique. La patiente ainsi que sa famille immédiate n'ont aucune histoire familiale de diabète ou de maladies coronariennes. La patiente nie l'utilisation abusive d'éthanol et l'utilisation de cocaïne. Elle n'a jamais souffert d'une maladie virale systémique, de tachycardie chronique non contrôlée, d'hypocalcémie, ou d'hypophosphatémie chronique. Un échocardiographie documente une dilatation marquée du ventricule gauche avec une réduction sévère de la fraction d'éjection à 20–25%. Un diagnostic de cardiomyopathie congestive sévère est alors posé. Une diète faible en sodium associée à l'administration de furosémide, de quinapril, et de métoprolol sont débutées. Deux jours suivant la cessation de la bromocriptine, l'état de la patiente s'améliore grandement tant au niveau symptomatique qu'au niveau des résultats répétés d'échocardiographie. Le traitement d'appoint de l'insuffisance cardiaque congestive est cessé après 15 jours, et la patiente n'a démontré aucune signe de récurrence des symptômes dans les 2 mois suivants. La bromocriptine n'est pas débutée à nouveau considérant certains aspects éthiques et la gravité de l'effet indésirable rencontré.

DISCUSSION: Bien que des effets cardiopulmonaires aient été rapportés avec la cabergoline, le cas décrit dans cet article représente à notre avis le premier cas publié de cardiomyopathie congestive sévère associée avec l'utilisation de la bromocriptine. Selon l'algorithme de Naranjo, le lien de causalité entre le développement de cette cardiomyopathie et l'utilisation de la bromocriptine est décrit comme probable.

CONCLUSIONS: La cardiomyopathie congestive est un effet secondaire sérieux qui peut être associé à l'utilisation de la bromocriptine dans le traitement d'un microprolactinome. Dans le cas présent, cet effet indésirable a été réversible suivant la cessation de la bromocriptine.

Sylvie Robert