Bromocriptine as a new therapeutic agent for peripartum cardiomyopathy

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ABSTRACT

Peripartum cardiomyopathy (PPCM) is a poorly understood, rare disorder in which left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum. Recent data suggest that uncontrolled oxidative stress leads to the activation of the prolactin cleaving enzyme cathepsin D that in turn leads to an increase in a cleaved 16 kDa prolactin. This cleaved form that has an angiostatic and proapoptotic role appears to drive the disease by adversely impacting the endothelium and cardiomyocyte. Bromocriptine that reduces the prolactin production by dopamine agonist actions may improve outcomes in patients with peripartum cardiomyopathy by eliminating the cleaved form of prolactin despite the activation of the cleaving enzyme. In limited case reports and proof of concept studies use of bromocriptine in the early stages has been shown to improve outcomes in patients with peripartum cardiomyopathy. However, larger randomized control study is still awaited.

Key words: 16 kDa prolactin fragment, bromocriptine, peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) is a disorder of unknown cause in which initial left ventricular systolic dysfunction and symptoms of heart failure occur between the last month of pregnancy and the first 5 months postpartum. Because of its rare incidence, the geographical differences and heterogeneous presentation, PPCM continues to be incompletely characterized and understood.

The clinical course of PPCM is highly variable and ranges from rapid progression to end stage heart failure (HF) to complete and spontaneous recovery of the ventricular function. Early signs and symptoms of PPCM mimic normal physiological findings of pregnancy including pedal edema and dyspnoea on exertion. Most patients develop symptoms in the first 4 months after delivery while 9% present in the last month of pregnancy. The most frequent initial presentation is with NYHA functional Class 3 or 4 symptoms, though some patients may present with complex ventricular arrhythmias.

The origins of this condition were unknown until recently and its treatment was empirical and restricted to standard heart failure therapy. The precise mechanisms that contribute to PPCM are still unclear though risk factors such as age (teenaged or older women), tocolytic therapy, number of children born, and malnutrition may identify sub groups of women with higher incidence.

Various pathogenic mechanisms have been suggested as triggering factors for PPCM and include low selenium levels, viral infections, stress activated cytokines, autoimmune factors, and the pathological response to hemodynamic stress. More recent experimental data suggests the involvement of a common pathway on which different etiologies induce PPCM merge. This cascade involves oxidative stress, the prolactin-cleaving protease cathepsin D and the hormone prolactin. Unbalanced oxidative stress seems to be the trigger that causes activation of protease cathepsin D, which cleaves the hormone prolactin into an angiostatic and proapoptotic 16 kDa form, which seems to drive the disease by impacting systemically on...
the endothelium as well as on the cardiac vasculature and cardiomyocyte function. Patients with acute PPCM have increased serum levels of oxidized low-density lipoprotein indicative of enhanced systemic oxidative stress, as well as increased serum levels of activated cathepsin D, total prolactin, and the cleaved angiostatic 16 kDa prolactin fragment.

In a mouse model, the 16 kDa prolactin fragment has been shown to have detrimental cardiovascular actions including inhibition of endothelial cell proliferation and migration, induction of endothelial cell apoptosis, and disruption of capillary structures. This form of prolactin also promotes vasoconstriction and impairs the cardiomyocyte function. High expression of 16 kDa prolactin, even in the absence of postpartum cardiomyopathy has been shown to destroy cardiac microvasculature, lower cardiac function, and promote ventricular dilatation. These effects of the 16 kDa form of prolactin are in contrast to the potential cardioprotective effects of full length prolactin to the maternal heart. 16 kDa prolactin does not act by means of the known prolactin receptors, indicating that its biological role is completely different from full-length prolactin.

An effective antioxidant defense mechanism in the maternal heart, late in pregnancy and in the postpartum period seems crucial as markers of cellular oxidation rise during pregnancy and experimental data in a mouse model of PPCM suggest that defective antioxidant defense mechanisms may be responsible for the development of this condition. Oxidative stress is a potent stimulus for the activation of cathepsin D and also of MMP-2, another enzyme able to generate the 16 kDa prolactin. Recently, there has been a close correlation documented between N-terminal brain natriuretic peptide (NT-proBNP, a marker of ventricular wall stress and heart failure), prolactin, and markers of oxidative stress (oxidized low-density lipoprotein) and inflammation (interferon-gamma), further supporting the detrimental role of the oxidative stress prolactin axis.

The ergot alkaloid Bromocriptine mesylate is a dopamine D2 receptor agonist that suppresses prolactin secretion, and to a lesser extent, activates D1 receptors. It also inhibits the release of glutamate, by reversing the glutamate GLT-1 transporter. Although a large fraction of the oral dose of bromocriptine is absorbed, only 7% of the dose reaches the systemic circulation because of a high rate and extensive first-pass metabolism in the liver. Other indications for bromocriptine use include hyperprolactinemia, Parkinson’s disease, pituitary tumors, neuroleptic malignant syndrome and has also recently been approved by FDA for the treatment of type-2 diabetes. Side effects of bromocriptine include nausea, vomiting, headache, and postural hypotension, particularly on initial use.

Following the concept that the cleaved form of the hormone prolactin initiates and drives PPCM, it has been hypothesized and studied that early pharmacological blockade of prolactin with bromocriptine may improve the condition of patients with acute onset of PPCM before irreversible damage occurs because of cell death, fibrosis, and remodeling. The apparent beneficial effect of bromocriptine results from eliminating the detrimental 16-kDa prolactin form, the harmful effects of which on the heart and vasculature have been described experimentally.

Apart from its prolactin blocking role, bromocriptine may exert “off target effects” in PPCM patients. Effects of bromocriptine on hemodynamic parameters in patients with heart failure were described 30 years ago before treatment with ACE inhibitors and beta blockers was routine. Positive effects of bromocriptine on blood pressure, vascular resistance, and plasma norepinephrine levels have been described. Beneficial effects of bromocriptine on the sympathetic nervous system and on hemodynamics may combine to assist recovery of PPCM patients.

Bromocriptine has been shown to affect metabolic parameters. In a study done by Kok et al., the acute effects of Bromocriptine on energy metabolism in obese women were analyzed. Mean 24-hour blood glucose and insulin were significantly reduced by Bromocriptine, whereas mean 24-hour plasma free fatty acid levels were increased, suggesting that lipolysis was stimulated. Bromocriptine was also shown to increase oxygen consumption and resting energy expenditure.

Several case reports of patients with newly diagnosed PPCM have shown that the addition of bromocriptine to standard therapy of HF may be beneficial in these patients. In a proof-of-concept randomized pilot study of patients with a newly diagnosed PPCM presenting within 4 weeks of delivery, patients receiving bromocriptine showed promising results. Patient receiving bromocriptine 2.5 mgs twice daily for 2 weeks, followed by 2.5 mgs once a day for 4 weeks, displayed greater recovery of left ventricular ejection fraction (27% at baseline to 58% at 6 months, P = 0.012) compared to patients assigned to standard care (27% at baseline to 36% at 6 months, NS). One patient in the bromocriptine treated group died compared with four patients in the placebo group. This proof-of-concept pilot study was performed in a group of homogenous patients in terms of ethnic background, age, time point of diagnosis, and baseline characteristics. Unfortunately, blinding of the study was not possible.
because the PPCM-standard group continued to nurse their infants while the PPCM-bromocriptine group could not breast feed because of bromocriptine induced cessation of lactation.

Bromocriptine has been used in postpartum women to stop lactation; however, this has been associated with several reports of myocardial infarction. Because of these, anticoagulation therapy is strongly encouraged in PPCM patients who are on bromocriptine.

Thus, bromocriptine has been found to be a promising drug for the treatment of PPCM; but before it is recommended as a routine strategy, there is a need for a larger randomized trial.

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Cite this article as: Chopra S, Verghese PP, Jacob JJ. Bromocriptine as a new therapeutic agent for peripartum cardiomyopathy. Indian J Endocr Metab 2012;16:S60-2.

Source of Support: Nil, Conflict of Interest: Nil.