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Pentoxifylline may be Potentially Harmful in the Treatment of Peripartum Cardiomyopathy

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Abstract

Introduction: Peripartum cardiomyopathy (PPCM) is associated with a significant rate of mortality and hence there is intense interest in identifying the etiology of this disease and determine therapeutic strategies. Heart failure in patients with PPCM has been associated with inflammation and significant rise in the plasma levels of pro-inflammatory cytokines. Pentoxifylline (PTX), a methylxanthine derivative, has been shown to possess anti-inflammatory, anti-apoptotic and rheological properties and therefore reasoned to be a good candidate as an add-on option in the therapy of PPCM.

Methods: We enrolled 80 PPCM patients. All received standard heart failure therapy. 41 patients were randomized to receive additional PTX and 39 received placebo. Clinical assessment, echocardiography and blood analysis were performed at baseline and after 6 months of therapy.

Results: Patients in the PTX group started off with a slightly worse New York Heart Association functional class (NYHA FC). All other parameters were similar at baseline and after 6 months of treatment. Overall mortality rate was low (6.25%), but among the 5 patients who died during the follow up period, 4 had been in the PTX group and only 1 in the placebo group.

Conclusions: Unexpectedly, we were not able to demonstrate improved mortality for PPCM patients through the addition of PTX 800mg TID to standard heart failure therapy. Rather it appears to be potentially harmful. In the absence of any demonstrable benefit for PPCM patients in this study and in the absence of other randomized trials on the subject, these results prompt us to underscore a note of caution against the use of PTX in addition to standard heart failure therapy in all PPCM patients, but especially in HIV-infected individuals with PPCM.

Keywords: Peripartum Cardiomyopathy; Pentoxifylline; Clinical Trials; Pregnancy; PPCM; PTX; Treatment

Introduction

Cardiomyopathy with reduced ejection fraction <45% that presents toward the end of pregnancy or in the months after delivery in a woman without previously known structural heart disease has been defined as peripartum cardiomyopathy (PPCM) [1]. While the mechanism(s) involved in the pathogenesis of this disease remains unknown, current research efforts are focused on the potential role of vascular dysfunction [2] and late-gestational maternal hormones [3] [4]. The prevalence of genetic mutations associated with familial dilated cardiomyopathy in a select number of patients with peripartum cardiomyopathy has also been suggested to play a role and thus it is reasoned that that there might be an overlap in the clinical spectrum of these two diseases [5] [6] [7], that are asymptomatic prior to pregnancy but become unmasked due to hemodynamic stress [4] and their respective forms of treatment. Another form of therapy is based on the finding that a deletion in the transcription factor termed Stat3 leads to the overexpression of cathepsin D, which cleaves prolactin into its cardiotoxic 16-kDa active form, thereby enhancing the anti-angiogenic and pro-apoptotic properties of prolactin that are instrumental in destroying cardiac and vascular tissues [3]. This has led to the use of a pharmacologic inhibitor of this process termed Bromocriptine that has shown some clinical benefit. Physiologic changes during pregnancy usually enhance maternal anti-oxidant defense mechanisms [8]. PPCM patients who show an improvement in their cardiac function exhibited a decrease in oxidized low density lipoprotein (oxLDL), a biomarker of oxidative stress [9].

As outlined above, while there has been progress made on the potential pathophysiologic mechanisms, the etiology of the disease remains unknown. Along these lines, there have been many potential causes of PPCM that have been proposed. These include viral myocarditis (infectious etiology), nutritional deficiencies, autoimmunity and micro-chimerism [10]. Increased plasma levels of a select number of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha), interferon-gamma, interleukin-6, C-reactive protein and Fas (apoptosis antigen 1 (Apo-1) have been thought to be a result of most of the above mechanisms and shown to play a role in the clinical outcome of patients with PPCM [11] [12] or idiopathic dilated cardiomyopathy [13]. This view has led to the rationale that perhaps agents with anti-inflammatory properties may be of clinical benefit in these patients. It was thus reasoned that pentoxifylline, a methylxanthine derivative may be a good add-on therapeutic candidate because it has been shown to have not only immune-modulatory, anti-inflammatory properties but also has anti-apoptotic and rheological properties [14] [15] as well as being an antioxidant [16]. These thoughts prompted an open-label non-randomized trial of pentoxifylline (PTX) as an add-on to standard cardiac function therapy for PPCM. The results of this study showed significant clinical benefit that has led to the common view among the clinical circles that such therapy should be utilized as a possible add-on therapy in patients with peripartum cardiomyopathy [17] [18]. However, plasma levels of inflammatory cytokines did not normalize using pentoxifylline at a dose of 400mg TID in PPCM patients [18] or in idiopathic dilated cardiomyopathy, presenting with severe decompensated heart failure [19]. Elevated circulating inflammatory cytokines including TNF-alpha have been associated with myocardial damage and reduced pump function, suggesting they may contribute to the deterioration of the heart [20]

Pentoxifylline has been used at a dose of 800mg TID in patients with AIDS for the inhibition of tumor necrosis factor production [21]. In the treatment of cryofibrinogenemia PTX has been successfully used at a dose of 800mg TID for 2 consecutive years [22]. The majority of described adverse effects (72%) were gastro-intestinal disturbances [23]. PTX 800mg TID has also been effective in accelerating the healing of leg ulcers and was well tolerated [24]. Even higher doses were used in patients with severe malaria to reduce plasma levels of TNF and IL-6 [25]. While previous studies on the effect of PTX in PPCM were open-label and non-randomized, the studies reported herein constitute a randomized and placebo-controlled study designed to objectively analyze the effect of pentoxifylline 800mg TID in addition to standard heart failure therapy in PPCM. As described below, unfortunately the results of the studies reported herein show distinct results. Such studies underscore the importance of conducting randomized placebo-controlled studies before arriving at therapeutic recommendations. This randomized placebo-controlled analysis aims to evaluate the effect of pentoxifylline in addition to standard heart failure therapy in PPCM.

Methods

Study design and patient recruitment

This study was approved by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand, Johannesburg, South Africa (PRC 990409) and complies with the

Declaration of Helsinki. All patients and controls gave written informed consent before study entry.

The study was conducted at Chris Hani Baragwanath Hospital, a tertiary institution located in Soweto, South Africa and linked to the University of the Witwatersrand, Johannesburg. It is the sole tertiary medical facility for this community. Patients were referred from local clinics, secondary hospitals, and the Department of Obstetrics at Chris Hani Baragwanath Hospital. History of pre-eclampsia and mode of delivery were obtained from the patient and confirmed by examining the obstetric card carried by each patient. The history of onset of symptoms and signs were recorded during first presentation at the cardiac clinic at Chris Hani Baragwanath Hospital (baseline) and after a follow-up period of six months (6 months visit). These were the two time points of the study. Clinical assessment, echocardiography and immune evaluation were performed at baseline and after 6 months of therapy.

Inclusion criteria: 1) age > 16 and < 40 years; 2) New York Heart Association functional class II – IV; 3) symptoms of congestive heart failure (CHF) that developed in the last month of pregnancy or during the first 5 months postpartum; 4) no other identifiable cause for heart failure; 5) left ventricular EF < 40% by transthoracic echocardiography; and 6) sinus rhythm. Exclusion criteria: 1) significant organic valvular heart disease; 2) systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 100 mmHg; 3) clinical conditions other than cardiomyopathy that could increase the studied inflammatory markers; 4) treatment with anti-inflammatory drugs; 5) severe anaemia (haemoglobin concentration <9gm/dl); and 6) metabolic disorders affecting lipoprotein metabolism i.e. thyroid disease.

The study included a total of 80 patients of which 39 were randomly assigned to the placebo group and 41 assigned to the pentoxifylline treatment group by the study co-ordinator. The codes were not released by the co-ordinator until completion of the studies for data analysis. Of these 80 patients, 27 were found to be HIV-1 positive, 11 of these 27 fell into the placebo group and 16 to the pentoxifylline group due to the randomized nature of the study.

All patients received treatment with diuretics and enalapril, an angiotensin-converting enzyme inhibitor. Patients with an EF ≤ 25% or LV thrombus received anti-coagulation therapy. Carvedilol was added after resolution of overt heart failure, and the dose was gradually titrated up to a target of 25 mg twice daily as long as SBP was ≥ 100 mmHg or symptoms such as dizziness did not occur. In addition, patients were randomized to receive either pentoxifylline 800 mg three times daily or a placebo medication. Following the initial screening and baseline visits, monthly outpatient visits were scheduled for clinical assessment and evaluation of medication compliance.

Echocardiographic studies, assessment of New York Heart Association functional class and non-invasive blood pressure measurements

All studies were performed and interpreted by the same two operators (A.Y. and A. B.) who were blinded to the protocol. Two-dimensional targeted M-mode echocardiography with Doppler color flow mapping was performed using a Hewlett Packard Sonos 5500 (Philips Ultrasound Inc., Bothell, Washington) echocardiograph attached to a 2.5 or 3.5 MHz transducer. Systolic and diastolic left ventricular dimensions were measured according to the American Society of Echocardiography guidelines [26]. Measurements of left ventricular dimensions and function were determined on an average of ≥ 3 beats.

A resident physician, who was provided with the clinical data, but blinded to the study protocol evaluated the NYHA Functional Classification of each patient during baseline and follow-up visits.

Heart rate, systolic and diastolic blood pressure were measured non-invasively with a Critikon Dinamap vital signs monitor 1846 and calculated as mean values from five readings. Measurements were made after a 30-minute resting period in sitting position with two-minute intervals between successive measurements.

HIV-1 testing

The study was conducted in a setting with high seropositivity for HIV-1 infection. Therefore, HIV-status was determined as part of the clinical treatment. Blood samples from each patient were tested for HIV-1 by standard PCR and anti-HIV antibodies screened using a commercially available enzyme-linked immunosorbent assay (ELISA) by the Clinical Laboratory of the Chris Baragwanath Hospital. Patients who were found positive by PCR were confirmed by a repeat PCR test. All PCR positive patients were positive for anti-HIV antibodies as determined by ELISA.

Peripheral blood CD4 levels

In efforts to determine a role for the relative immune status at the time of enrollment (baseline) and following 6 month follow up, blood samples were analyzed for the frequencies of CD4+ T cells using standard flow cytometry with a FACSCAN (BD Flow Cytometry, Mountain View, CA) by the clinical laboratory at the Chris Hani Baragwanath Hospital.

Statistical analysis

Data were analyzed using the Analyse-it Standard edition version 5.50 statistical program (Analyse-it Software, Leeds, United Kingdom). Results are expressed as mean values. We used Anova for comparison between patients who were randomized to Placebo vs. Pentoxifylline at baseline and after 6 months of therapy. Fisher's Exact Test was applied to analyze the difference in mortality between the patients who received placebo and the patients that received Pentoxifylline . Significance was assumed utilizing a two-tailed value of $P< 0.05$.

Results

As seen in Table 1, patients who received standard heart failure therapy had similar baseline characteristics compared with those who received additional therapy with pentoxifylline (PTX). The only difference was that the initial NYHA functional class was slightly higher among those who received PTX. No patient had a history of drug abuse, but 2 were regular smokers and one a regular consumer but with no history of alcohol abuse. One patient had a history of pre-eclampsia during a previous but not during the recent pregnancy. Two patients had previously experienced a stillbirth. 1 patient had an episode of PPCM during a previous pregnancy. None of the above patients died during the 6 months follow-up period.

Patient characteristics and parameters assessed	**Standard therapy Mean +/- S.D. N = 39**	**Standard therapy+ PTX Mean +/- S.D. N = 41**	**p-value**
Age	28.8±7.7	30.7±7.1	0.29
NYHA FC	3.1±0.6	3.4±0.6	0.032
Pulse rate/min	100.4±16.3	102.3±21.4	0.68
DBP (mmHg)	74.2±10.2	76.0±14.3	0.53
SBP (mmHg)	110.1±16.4	115.2±20.5	0.26
LVESD (mm)	48.5±6.0	49.2±6.5	0.57
LVEDD (mm)	56.2±5.8	57.2±6.1	0.38
LVEF (%)	29.9±8.0	29.1±9.4	0.65

After 6 months of therapy a total of 5 of the 80 (6.25%) patients had died while receiving treatment and 4 moved to remote areas and were lost to follow up. Additionally, one was reported dead after defaulting therapy for 1 month and another one defaulted but was found alive and well 3 years later and thus lacked the 6 months evaluation data. Unexpectedly PTX did not improve survival. As seen in Table 2, while only 1/ 39 died under standard therapy, 4/ 41 died in the PTX addon therapy group. When the Fisher's exact test was applied, the differences between the patients who received placebo versus those that received Pentoxifylline was not significant. However, the trend is clearly apparent. There did not appear to be any significant difference in cardiac function between the standard therapy group as compared with the cohort that received pentoxifylline as an addon therapy. Although, the numbers are small, the important issue here is that there appeared to be a tendency for lack of a therapeutic effect and poor clinical outcome through the addition of PTX to standard heart failure therapy.

Table 2: Results of the studies at 6-months

Patient characteristics and parameters assessed	Standard therapy N = 35	Standard therapy+ PTX N = 33	p-value
Deceased	1	4	0.36
NYHA FC	1.5±0.7	1.5±0.7	0.75
Pulse rate/min	81.5±13.5	87.8±19.3	0.19
DBP (mmHg)	70.8±11.5	71.8±13.2	0.72
SBP (mmHg)	107.5±13.8	110.0±17.1	0.52
LVESD (mm)	39.7±8.0	40.5±8.2	0.65
LVEDD (mm)	50.1±8.2	52.6±7.2	0.18
LVEF (%)	42.3±10.5	46.8±11.4	0.11

None of the 80 patients in this study had a previous medical history of diabetes. However, 4 of them had elevated random blood glucose levels at baseline that were above normal but not enough to establish a diagnosis of diabetes (7.8 / 9.5 / 9.5 / 10.7 mmol/l). All of them had been randomized to PTX. Two were alive and had normal glucose levels at follow-up while unfortunately the other 2 had died. They were both HIV-negative and had very poor cardiac function at baseline: One had an ejection fraction (EF) of 18% with a left ventricular end diastolic diameter (LVEDD) of 61mm and the other one had an EF of 26% with a LVEDD 64mm.

Role of HIV on response to pentoxifylline addon therapy

As stated in the Methods section above, of the 80 patients included in this study, 27 were found to be HIV-1 positive at baseline, 11 of these 27 were assigned to the placebo group that included 39 patients and 16 assigned to the pentoxifylline group that included 41 patients. There were no new infections during the 6 month follow up period. As expected, there was a significant ($p< 0.0001$) difference in the absolute numbers of CD4+ T cells (Mean +/- S.D) in patients who were HIV-positive at baseline as compared with the HIV-1 negative cohort (432.6 +/- 293.7 v/s 1013.6 +/- 412.9). At the 6-month follow up time period, the values did not change significantly within the HIV-1 positive (from 432.6 +/- 293.7 as compared with 375.3 +/- 274.6 at 6 months) versus HIV-1 negative cohorts (1013.6 +/- 412.9 as compared with 777.0 +/- 236.2 at 6 months). We reason that HIV-1 infection did not appreciably change the immune status of the infected patients during the 6 month follow up period at least as measured by absolute CD4 count measurements. The other question obviously was whether HIV-1 status contributed to the therapeutic response to pentoxifylline. We have previously documented that there is indeed no statistical difference on the clinical outcome of HIV-1 infection in PPCM patients based on analysis of the data on cardiac function [27]. We submit that although the number of patients in each group are low, there did not appear to be any role of HIV-infection in this cohort.

Discussion

Pentoxifylline is a methyl-xanthine derivate that inhibits phosphodiesterase IV [28]. It has three major properties that include improving the rheological properties of blood, it has anti-inflammatory and antioxidative properties [29]. PTX improves the rheological properties of blood through peripheral vasodilatation, improvement of erythrocyte flexibility [30], reduction of platelet aggregation [31] and blood viscosity as well as improvement of the microcirculatory blood flow [32].

PTX is also an inhibitor of pro-inflammatory cytokines, such as TNF-alpha and inhibits apoptosis in different human cell lineages in vitro [33] and in vivo [34]. High plasma TNF-alpha levels and increased apoptosis of cardiac cells may contribute to disease progression and mortality in heart failure [35] [34].

Because PTX is considered safe and very well tolerated [36] [37] [38], it has been used as an ideal anti-inflammatory agent for chronic inflammatory conditions. The vasodilatory, anti-inflammatory and anti-apoptotic properties of PTX was thus considered as a prime candidate for the treatment of heart failure [39]. PTX related significant adverse events are very rare [40]. A meta-analysis evaluating PTX versus placebo in heart failure

suggested a significant (nearly fourfold) decrease in all-cause mortality in the PTX group [41].

In the present study, overall mortality was considerably lower (6.25%) than reported in previous studies on PPCM [42] [18] [43] from the African region (12.3%, 15% and 18.7% respectively) and is more in keeping with a recent ESC EORP registry that reports an overall mortality in PPCM of 6% [44] when combining data from different regions of the world. It must be kept in mind however, that there are more therapeutic options like cardiac assist devices or heart transplantation in highly developed countries. These were clearly not a viable option in our study population for obvious reasons. Improved mortality rate in this study might be due to increased awareness among local referring physicians about the existence of PPCM as a distinct disease entity [45] as well as general progress in the treatment of heart failure. It stands out that among the 5 patients who died in this trial, 4 were on PTX in addition to standard heart failure therapy.

Recently, Koczo et al. reported that an increased immune-modulatory response represented by increased serum levels of soluble interleukin IL-2 and IL-4 seems to be protective in PPCM. [11] Possibly the addition of PTX to standard heart failure therapy caused interference with IL-2 expression levels [46] and therefore contributed to poor outcome. Two of the 4 patients who died in the PTX group had elevated random blood sugar levels at baseline but did not have an established diagnosis of diabetes. We therefore conducted a PubMed research to identify possible negative effects of PTX on glycemic control. However, the results of this search indicated that in fact there is a beneficial role of PTX. Thus, Han et al. report that PTX improved glucose control and is a potential therapeutic alternative for treating diabetes [47]. A meta-analysis by Tian et al. found that PTX can provide additive anti-proteinuric effect in diabetics [48] when given in combination with angiotensin-converting enzyme inhibitor (ACE-I) as we have done in the study reported herein. Finally, Ravera et al. found that the administration of statins, PTX, sulodexide, and the inhibition of the renin-angiotensin-aldosterone system seems to be a promising way to preserve renal function in diabetic nephropathy [49].

In the present study, there was a total of 27 HIV-positive PPCM patients, out of those 2 passed away during the follow-up period (7.4%), both of whom were on PTX in addition to standard heart failure therapy. PTX has several immune-modulatory and anti-viral properties which could be of benefit against HIV-1 at various levels [50]. PTX has been used as supportive treatment of HIV-infection as it decreases human immunodeficiency virus type 1 (HIV-1) replication [51] and TNF-alpha levels which interfere with the anti-retroviral activity of zidovudine (AZT) [52]. Furthermore, it has been shown that PTX can directly reduce HIV-associated pro-inflammatory endothelial cell activation, which may underlie vascular dysfunction and coronary vascular disease [53]. However, other authors report the complete opposite, namely that PTX did not improve endothelial function and unexpectedly increased inflammatory biomarkers in HIV-infected patients [36] [54]. PTX has also been recommended as a form of supportive treatment in advanced HIV infection [55]. Cytokine dysregulation in HIV-1 infection has been documented in numerous studies and has been cited as an important component in the pathogenesis of HIV. Therefore the use of PTX as addon therapy has been suggested in the treatment of patients with HIV-1 infection [56]. We recognize that HIV-1 infection in this patient population is a confounding variable. Considering the beneficial effects of PTX therapy in HIV-1 infected patients as discussed above, the fact that we noted poor outcome in PPCM patients, makes the role of HIV-1 infection in the PPCM patients an irrelevant factor.

In conclusion, overall mortality in this study was lower (6.25%) than in other trials reporting on PPCM patients under similar conditions (12.3% and higher) [18] [42] [43]. However, we were not able to demonstrate improved mortality for PPCM patients through the addition of PTX 800mg TID to standard heart failure therapy. Rather it appears to be potentially harmful. In the absence of any demonstrable benefit for PPCM patients in this study and in the absence of other randomized trials on the subject, these results serve as a caution against the use of PTX in addition to standard heart failure therapy in all PPCM patients, but especially in HIV-infected individuals with PPCM.

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