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Pentoxifylline Fails to Prevent the Jarisch-Herxheimer Reaction or Associated Cytokine Release

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The Jarisch-Herxheimer reaction (JHR) observed after antibiotic treatment of relapsing fever caused by *Borrelia recurrentis* is associated with the systemic appearance of cytokines. The decrease of cytokine production and block of JHR was attempted by administering pentoxifylline prior to antibiotic treatment. Fifteen patients with confirmed relapsing fever were infused intravenously with pentoxifylline 90 min before intramuscular injection of penicillin; 4 patients were not treated with pentoxifylline. All patients developed JHR to varying degrees. Treatment with pentoxifylline failed to prevent fever, increase in pulse, respiration, or blood pressure, or decrease in white blood cell count. No reduction of circulating levels of tumor necrosis factor, interleukin 6, or interleukin-8 was observed with pentoxifylline treatment. Pentoxifylline did not prevent clearance of the *B. recurrentis* spirochetes. Thus, pentoxifylline treatment of patients with relapsing fever fails to prevent or diminish JHR or the associated cytokine release observed after appropriate antibiotic treatment.

The Jarisch-Herxheimer reaction (JHR) is a severe systemic reaction observed after treatment of spirochete infections, although it can be observed after treatment of other bacterial infections. The reaction consists of a rise in temperature, a decrease in white blood cell count, and a rise in pulse and respiration rates. While it occurs after treatment of many spirochete infections, the most severe reaction occurs after treatment of relapsing fever [1].

Relapsing fever is due to the bloodborne spirochete, *Borrelia recurrentis*. The spirochete is spread from host to host by ticks or lice and is endemic in eastern Africa. The disease results in recurring fevers with relapses every 3–5 days. Relapsing fever carries a high mortality rate if left untreated; however, standard antibiotic therapy induces JHR in up to 40% of treated patients [2].

We have previously reported that JHR is associated with the systemic release of cytokines [3]. Many reports have implicated the acute production of cytokines as the causative factors for the altered pathophysiology observed in several diseases. In this study, we sought to reduce the production of cytokines by pretreating patients with pentoxifylline, which has been re-

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ported to decrease cytokine production [4]. The treatment protocol tested whether pentoxifylline could reduce the production of cytokines in the face of JHR and thereby lessen its clinical symptoms.

Materials and Methods

Selection of patients and treatment protocol. Patients were identified at the Tikur Anbessa and Black Lion Hospitals, Addis Ababa University, by a history of fever, headache, and chills. A definitive diagnosis of relapsing fever was made by identification of the spirochetes in a Giemsa-stained peripheral blood smear. The duration of the symptoms, age, sex, and clinical parameters were determined by the clinical history of the patient. Of 19 patients identified, 15 were treated with pentoxifylline immediately prior to antibiotic treatment and 4 were treated with antibiotics alone. One of the pentoxifylline-treated patients was excluded from subsequent analysis because spontaneous lysis of the spirochetes occurred prior to antibiotic treatment. After intravenous pentoxifylline was given in a loading dose of 300 mg over 90 min, the relapsing fever was treated with 600,000 U of penicillin intramuscularly. This intravenous dose of pentoxifylline has been shown to decrease tumor necrosis factor (TNF) production in response to endotoxin [4]. Pentoxifylline treatment was continued by intravenous infusion for 16 h at a dose of 40 mg/h. Each patient subsequently received oral tetracycline (250 mg four times a day) for 3 days to ensure treatment success.

Data collection. Blood samples were collected at the following times: −1.5 h (prior to the start of pentoxifylline infusion), 0 h (before initiation of antibiotic treatment), and 1, 2, 3, 5, 8, and 24 h. Clinical data were collected at the same time points for blood pressure, pulse, respiration rate, and temperature. Blood was processed for white blood cell count, and a blood smear was examined to document the elimination of the spirochetes, defined as the absence of spirochetes in 50 microscopic fields. Plasma was obtained immediately and frozen for later cytokine analysis.

Cytokine analysis. Cytokines were measured as in our previous study [3]. Briefly, TNF was determined by the WEHI 164 subclone 13 biologic assay, interleukin (IL)-6 was measured by the B9 biologic assay, and IL-8 was measured with a sensitive and specific ELISA, which measures only IL-8 and not other chemokines, such as Groα, RANTES, or MIP-1.

Statistical analyses. Results between the groups were first compared by analysis of variance. Differences between the individual groups were then compared by Student's Newman-Keuls test. These analyses were done only with the pentoxifylline-treated patients, since there were too few non–pentoxifylline-treated patients for appropriate analysis.

Results

Presenting clinical signs and symptoms. The clinical data on patients presenting with relapsing fever are shown in table 1. All of the patients presented with headache and fever, and the majority also had chills. For all patients, a definitive diagnosis of relapsing fever was made by direct visualization of spirochetes in the blood smear. At the time of admission into the study, all patients were tachypnic (32 ± 2 breaths/min) and tachycardic (119 ± 4 beats/min) and had an elevated temperature (39.1 ± 0.2°C). For this analysis, both the pentoxifylline-treated and -untreated patient data were combined because the groups were similar until the infusion of pentoxifylline. Symptoms were present for 2–12 days prior to treatment.

Table 1. Clinical data for patients presenting with relapsing fever who were subsequently treated or not treated with pentoxifylline prior to administration of antibiotic for the infection.

	Pentoxifylline pretreatment	
	Yes	No
Male:female	13:1	4:0
Age (years)	24 (13–45)	21 (14–28)
% with symptoms		
Headache	100	100
Fever	100	100
Chills	71	100
Duration (days) of symptoms	4.4 (3–8)	7 (2–12)
No. (%) with blood smear positive for spirochetes	14 (100)	4 (100)
No. (%) with JHR	14 (100)	4 (100)
Mild	4 (29)	1 (25)
Moderate to severe	10 (71)	3 (75)
Time (h) to onset of JHR	1.6 (1.33–2)	1.5 (1.17–2)
Peak temperature (°C)	40.7 ± 0.2	40.8 ± 0.4
Peak pulse (beats/min)	137 ± 6	152 ± 4
Peak respiratory rate	44 ± 3	44 ± 3
Time (h) to clearance of spirochetes after antibiotics	4.6 (3–8)	6.0 (5–8)

NOTE. JHR, Jarisch-Herxheimer reaction. Data are mean ± SE or mean (range) unless indicated as %. There was no difference between pentoxifylline and no pentoxifylline groups for any parameter.

Development of JHR. Fourteen of the study patients were given intravenous pentoxifylline prior to treatment with intramuscular penicillin; an additional 4 patients were treated with penicillin only. All of the patients in this study developed JHR, and the prior administration of pentoxifylline did not decrease the incidence or severity of the reaction. The assessment of severity of the reaction was based on the clinical observations of vomiting, loss of continence, and development of chills and rigor. Severity was classified as moderate to severe in 71% of the patients treated with pentoxifylline and 75% of patients not given pentoxifylline. JHR was defined quantitatively (table 1). A classic feature of JHR is pyrexia, which develops even in the face of elevated temperature due to the underlying disease; the data in table 1 show that all of the patients had a rapid increase in temperature that was not inhibited by pentoxifylline.

After antibiotic treatment of relapsing fever, temperatures returned to normal within 24 h in all patients (36.7 ± 0.1°C). Both pulse and respiration rates increased significantly after antibiotic treatment and were unaffected by prior infusion of pentoxifylline (table 1). All of these clinical parameters during the acute phase of the disease (−1.5 to 8 h) were significantly

elevated above those observed after successful treatment of the relapsing fever (24 h). The mean arterial blood pressure also increases during JHR as the white blood cell count falls. We observed both of these changes in our patients within 1–2 h after antibiotic treatment; again, pentoxifylline failed to prevent these parameters from changing (data not shown). While pentoxifylline treatment did not prevent JHR, it also did not interfere with clearance of the spirochetes, since the blood smears showed clearance of spirochetes within 8 h of antibiotic treatment (table 1).

Alterations in cytokine levels. We first reported during the 1989 season of relapsing fever, in the same clinical setting as the current study, a dramatic increase in the appearance of cytokine levels as JHR evolves [3]. The appearance of TNF, IL-6, and IL-8 over time was measured in the previous study. In our present study, all of the patients developed JHR and all had an increase in circulating cytokine levels. To directly compare the appearance of the cytokines in patients pretreated with pentoxifylline with those not pretreated, plasma cytokine profiles from the 1989 relapsing fever season are also presented [3]. Data for each patient are expressed as a percent of that patient's maximal response in order to normalize the data. Figure 1 shows that there was no significant inhibition of any of these cytokine levels by pentoxifylline. In fact, the curves are nearly superimposable with regard to the kinetics and magnitude of the cytokine response. As in many other studies, TNF is the first cytokine to appear, with IL-6 and IL-8 lagging slightly behind. TNF was rapidly cleared from the blood and by 5 h had nearly returned to baseline levels. It should be noted that the TNF in these patients was measured with a bioassay; therefore, the TNF in the bloodstream represents biologically active TNF and not inactive TNF complexed with soluble receptors. By 24 h, TNF, IL-6, and IL-8 were detectable in only 3 of the 18 patients; for all three cytokines, the levels were significantly less than peak levels.

Discussion

Cytokines have been implicated in the pathogenesis of a wide spectrum of diseases, including sepsis, autoimmune diseases, and transplant rejection. It has been suggested that inhibition of the production of cytokines may prove a useful therapeutic modality for the treatment of these diseases. Many experimental approaches have been tried to inhibit either the production or action of cytokines and thereby improve outcome. These treatment options may work very well during in vitro testing conditions or in experimental animal models of disease but then fail to show efficacy in clinical trials. There remains a critical need to better understand the basic mediators of disease and to investigate the efficacy of drugs proposed as new therapeutic agents.

Pentoxifylline has been used extensively in animal studies, in which contradictory results are often observed. Using the lipopolysaccharide (LPS) model of sepsis, pentoxifylline has

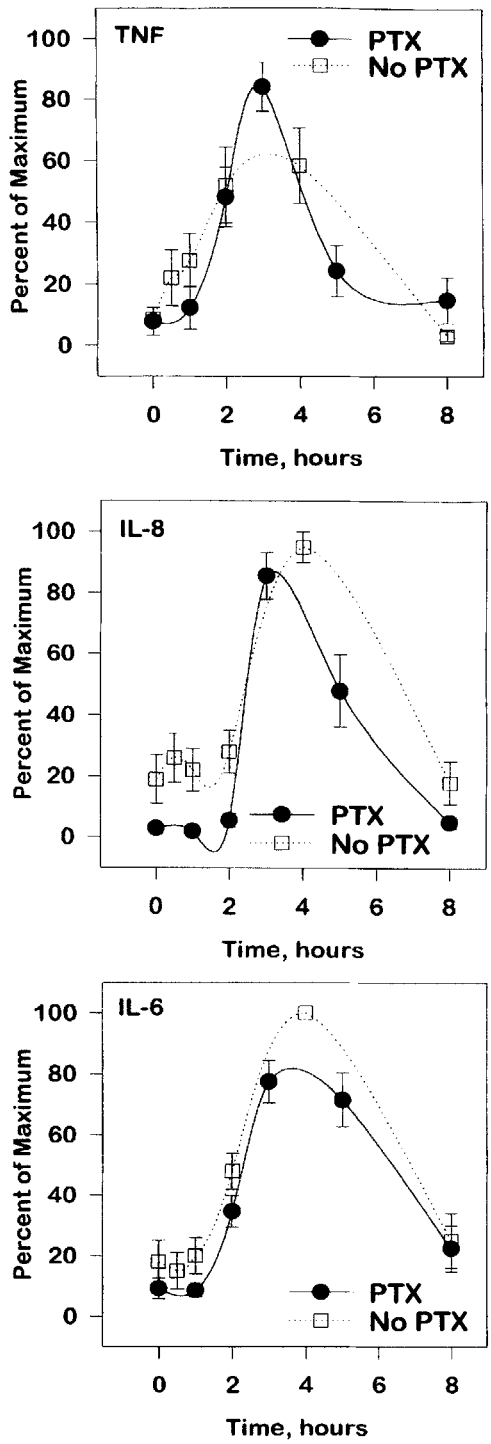

Figure 1. Increases in circulating cytokine levels during Jarisch-Herxheimer reaction. Circulating cytokine levels (interleukin [IL]-6 and -8 and tumor necrosis factor [TNF]) were measured and expressed as % of each patient's maximum value. Pentoxifylline (PTX) levels are from this study, while no PTX levels were determined during previous year. All 3 cytokines showed dramatic increase that was not blunted by pentoxifylline. Each value is mean ± SE for 13 to 14 patients in pentoxifylline group and 15 in no pentoxifylline group.

been reported to decrease TNF production and improve survival [5]; however, in another study, TNF production was reduced but there was no improvement in survival [6]. Conflicting results have also been reported in pig models of peritonitis: In one study, pentoxifylline was reported to have beneficial effects [7]; another study reported limited beneficial effects and specifically documented that pentoxifylline did not reduce TNF levels [8]. Pentoxifylline failed to prevent microvascular injury in a rat model of peritonitis [9].

Despite these negative or conflicting results in experimental animals, pentoxifylline has been proposed as a treatment for several diseases because it has been effective in reducing TNF production in LPS-stimulated cells while increasing IL-6 levels [10]. This differential inhibition of cytokine production is also observed when pentoxifylline is ingested orally and the isolated mononuclear cells are stimulated with LPS [11]. Inhibition of TNF was noted when malaria antigens were used to stimulate human or murine cells [12].

It has been reported that there was no reduction in the side effects of OKT3 therapy when patients were given pentoxifylline [13]. In another study using endotoxin-infused healthy volunteers as a model for sepsis, pentoxifylline reduced the appearance of TNF in the serum but did not reduce IL-6 or cortisol levels [4]. Additionally, none of the clinical responses to endotoxin were blocked. Another study using oral pentoxifylline prior to infusion of endotoxin failed to show any reduction in fever or plasma cytokine levels [14]. Our results are very similar to these studies [4, 13, 14] in several respects.

First, pentoxifylline did not prevent any of the clinical manifestations of JHR from appearing. Second, treatment of the underlying disease (transplant rejection or relapsing fever) was not affected by pentoxifylline. Third, we did not observe any reduction in IL-6 levels with pentoxifylline treatment. However, we also did not detect any reduction in TNF production after treatment of relapsing fever, while TNF was reduced in some of the previous studies [4]. The stimulus for the cytokine release in JHR is not known, but it is clearly related to rapid spirochete removal from blood, resulting in overwhelming stimulation of the reticuloendothelial system. It is possible that pentoxifylline will not block stimulation of cells other than monocytes [15] or that different stimuli are not affected by pentoxifylline.

These conflicting human and animal studies highlight the need for continued investigations. Future studies must determine if there is a reduction in the clinical parameters of the disease, if there are any alterations in the mediators felt to be responsible for the disease, and if treatment of the underlying disease has still been successful. Our data clearly indicate that pentoxifylline will not prevent acute physiologic changes associated with spontaneous release of cytokines. The use of JHR of relapsing fever as a human model of cytokine release gives a highly reproducible model of terms of severity and kinetics.

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