ORIGINAL ARTICLE

Effect of Pentoxifylline on Tumor Necrosis Factor-Alpha and Interleukin-6 Levels in Neonatal Sepsis

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Summary

Several pharmacological agents have been found to alter systemic concentrations and/or the activity of different cytokines via a variety of mechanisms, including changes in biosynthesis, secretion, and/or stability. Pentoxifylline (PTX), which is a methylxanthine derivative for example, has multiple effects on the immune system, but inhibition of pro-inflammatory cytokine release predominates. In this study we aimed to evaluate the influence of PTX on plasma levels of tumor necrosis factor (TNF) alpha and interleukin (IL)-6 in newborn infants with sepsis. The study included 20 infants with neonatal sepsis. In all subjects blood samples for serum C-reactive protein, TNF alpha and IL-6 determinations were received before giving PTX and at the 12th and 24th hours following PTX. In addition, white blood cell was counted before giving PTX and on the 3rd and 7th day following PTX. The infants were randomly divided into two groups. Firstly, PTX was used in infants who were successively admitted to the clinic and the subsequent infants were accepted as a control group. Of 20 infants, 13 infants received PTX and seven infants did not. We did not find any difference in the leukocyte count, serum C-reactive protein level, TNF alpha and IL-6 levels between the two groups of patients ($P > 0.05$). While three infants died in the group of receiving PTX, death was not recorded in the group of non-receiving PTX ($P > 0.05$). Our findings showed that PTX treatment did not affect leukocyte counts, serum CRP levels, TNF alpha and IL-6 levels and death ratio in newborn infants with sepsis. The last result may be due to the fact that the number of patients in the study was very small. We think that more extensive and controlled studies should be performed about this subject.

Key Words: Pentoxifylline, Newborn, Sepsis

Introduction

Cytokines are proteins that are produced by immune and non-immune cells and they function as mediators to facilitate cellular communication. Their production is regulated by a complex network of co-stimulatory and feedback loops that responds to a variety of stimuli. Several pharmacological agents have been found to alter systemic concentrations and/or the activity of different cytokines via a variety of mechanisms, including changes in biosynthesis, secretion, and/or stability[1]. Pentoxifylline (PTX), which is a methylxanthine derivative for example, has multiple effects on the immune system, but inhibition of pro-inflammatory cytokine release predominates[1,2]. Several studies have been performed to determine the relationship between tumor necrosis factor (TNF), interleukins (IL) and sepsis, but the results are contradictory [3-6]. In this study, we aimed to evaluate the influence of PTX on plasma levels of TNF alpha and IL-6 in newborn infants with sepsis and to assess the effect of this immunomodulating drug on the clinical outcome in these infants.

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Materials and Methods

The study included 20 infants with neonatal sepsis. The study was carried out in the Division of Neonatology, Faculty of Medicine, Erciyes University, Kayseri, Turkey. Inclusion criteria included symptoms and signs of infection and respiratory or cardiovascular dysfunction. Symptom and signs of infection were defined by the presence of at least two of the following: feeding intolerance, abdominal distension, lethargy, irritability, temperature instability, hyperbilirubinaemia and hepatosplenomegaly[5]. In all subjects blood samples for serum C-reactive protein, TNF alpha and IL-6 determinations were received before giving PTX and at the 12th and 24th hours following PTX. In addition, white blood cell was counted before giving PTX and on the 3rd and 7th day following PTX. PTX was supplied by Hoechst Company, Istanbul, Turkey. Serum TNF alpha and IL-6 concentrations were measured by enzyme linked immunosorbent assay method. Aside from supportive treatment, a combination of cephalosporin plus aminoglycoside was initiated in all infants, but antibiotics were changed in accordance to the antibiogram or on clinical ground. The infants were randomly divided into two groups. Firstly, PTX was used in infants who were successively admitted to the clinic and the subsequent infants were accepted as a control group. PTX was initiated 0.5 hour before beginning antibiotic therapy and given in a dose of 0.5 mg/kg/h by continuous infusion for 24 hours. The dose was not repeated. For this study, permission was received from the infants' parents and the ethics committee of the hospital. Statistical analyses were performed by using Mann-Whitney U - Wilcoxon Rank Sum W test and Chi Square test.

Results

Of 20 infants 13 (nine boys and four girls) infants received PTX and seven (four boys and three girls) infants did not. There was no significant difference in boy:girl ratio between the groups (χ^2: 2 ; P >0.05) (Table I). There was no significant difference in age on admission, gestational age, weight and boy:girl ratio between the groups (P >0.05). In addition, we did not find any difference in the leukocyte count and the levels of serum CRP, TNF alpha and IL-6 between the groups receiving PTX and non-receiving PTX (P >0.05) (Table I). However, the CRP values of the control subjects were higher than those of the study group throughout the study period. The initial TNF values of the study group were higher than those of the control group. In addition the TNF values in the study group appeared to have declined precipitously when compared with the control group (Table I). Blood culture was positive in 12 (60%) infants. The microorganisms isolated from blood culture were as follows: *Staphylococcus epidermidis* in five (41%) infants, *Eschericha coli* in two (16.5%), Enterobacter in two (16.5%), Klebsiella in two (16.5%) and Enterococcus in one (9.5%). While three infants died in the group of receiving PTX, death was not recorded in the group of non-receiving PTX (X^2: 4; P >0.05).

Table I: Clinical and laboratory findings of the infants

Parameters	Patient Group (n = 20)		Z	P
	Receiving PTX (n = 13)	Non-receiving PTX (n = 7)		
Age at admission (day)	4.38 ± 3.64	9.23 ± 8.71	-1.11	>0.05
Gestational age (week)	37.62 ± 2.43	38.00 ± 2.08	-0.24	>0.05
Weight (g)	2509 ± 549	2822 ± 637	-0.91	>0.05
Leukocyte count (mm^3)				
At beginning	11,192 ± 5817	13,014 ± 6688	-0.43	>0.05
3^{rd} day	12,461 ± 7390	12,528 ± 6173	-0.03	>0.05
7^{th} day	14,615 ± 4777	15,185 ± 6634	-0.55	>0.05
Serum CRP level (mg/dl)				
At beginning	40 ± 105	71 ± 84	-0.99	>0.05
12^{th} hour	43 ± 106	86 ± 96	-1.66	>0.05
24^{th} hour	44 ± 102	61 ± 69	-0.95	>0.05
Serum TNF alpha (pg/ml)				
At beginning	205 ± 357	75 ± 58	-0.19	>0.05
12^{th} hour	51 ± 27	56 ± 48	-0.19	>0.05
24^{th} hour	44 ± 40	30 ± 24	-0.63	>0.05
Serum IL-6 (pg/ml)				
At beginning	254 ± 341	361 ± 431	-0.55	>0.05
12^{th} hour	199 ± 233	307 ± 417	-0.11	>0.05
24^{th} hour	153 ± 262	234 ± 316	-0.79	>0.05

Discussion

Several studies have been performed to determine the relationship between cytokines and neonatal sepsis in the literature[7-10]. Most of them revealed that both plasma IL-6 and TNF-alpha levels were significantly higher in patients with neonatal sepsis than in controls [8-10]. Based on these data de Bont et al. [9] and Silveira et al.[10] noted that the combination of TNF-alpha and IL-6 determinations appeared to be a good predictor of neonatal sepsis. Harris et al.[7] noted that plasma IL-6 level is a more reliable indicator of bacterial sepsis and necrotizing enterocolitis than plasma TNF and IL-6 levels were also significantly higher in nonsurvivors than in survivors ($P < 0.001$). In contrast, plasma TNF values were not consistently increased in any of the groups [7]. In our study, we did not find any difference in the leukocyte count and the levels of serum CRP, TNF alpha and IL-6 between the groups receiving PTX and non-receiving PTX.

The growing knowledge on the pathophysiological role of cytokines in septic shock stimulated efforts to control their synthesis and action pharmacologically in clinical situations. TNF has a pivotal role in the pathogenesis of sepsis and septic shock. Suppression of its biosynthesis might therefore be one of the strategies in the treatment of sepsis [3,11]. It was shown that TNF and IL-6 producing capacities were higher in septic patients than in healthy subjects. PTX inhibited TNF production, but only a moderate inhibitory effect was observed on the induction of IL-6 [3]. Zeni et al.[4] found that PTX was able to decrease serum TNF but not IL-6 or IL-8 serum concentrations during septic shock. In contrast to these, Lauterbach et al. [5,6] found that PTX significantly affected the synthesis of TNF and IL-6 as well as reduced the mortality rate in premature infants with sepsis. Our findings showed that PTX did not affect leukocyte count, serum CRP level, TNF alpha and IL-6 levels and death ratio in newborn infants with sepsis. This could have been related to that the small number of patients in the study. We think that more extensive and controlled studies should be performed about this subject.

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