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Effect of an Interleukin-1 Receptor Antagonist on the Hemodynamic Manifestations of Group B Streptococcal Sepsis

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ABSTRACT

IL-1 is purported to be a proximal mediator in the cascade leading to septic shock. To characterize its hemodynamic effects and to ascertain whether its blockade would ameliorate the deleterious consequences of sepsis, an IL-1 receptor antagonist (IL-1ra) was administered to 16 anesthetized, mechanically ventilated piglets that received a continuous infusion of group B streptococci (GBS) (7.5×10^7 colony-forming units/kg/min). Systemic (Psa), pulmonary artery (Ppa), and wedge (Pwp) pressures and cardiac output were measured pre-GBS and every 30 min during GBS infusion. After 15 min of bacterial infusion the control group received normal saline, whereas the treatment group received a bolus of IL-1ra (40 mg/kg) followed by a continuous infusion of IL-1ra (60 μg/kg/min). In comparing IL-1ra-treated animals with controls from the 15-min GBS baseline to the succeeding septic study period (45–120 min), the following treatment effects were noted (120-min values shown): mean Psa remained elevated in treatment compared with control animals (12.7 ± 2.5 *versus* 9 ± 3.5 kPa; $p < 0.001$) as did CO (0.21 ± 0.07 *versus* 0.13 ± 0.08 L/min/kg; $p < 0.001$). Pwp decreased in the treatment compared to the control group over the study period (1 ± 0.3 *versus* 1.6 ± 0.7 kPa; $p < 0.02$). Mean Ppa and mean Pra were not different between groups over time. Median length of survival was significantly longer ($p = 0.04$) in treated (226 min) compared with control animals (150 min). These data suggest that IL-1 plays an important role in GBS sepsis and septic shock, and that IL-1ra may in part ameliorate the cardiovascular alterations associated with GBS sepsis in the neonate. (***Pediatr Res* 38: 704–708, 1995**)

Abbreviations

CO, cardiac output
GBS, group B streptococci
IL-1ra, human recombinant IL-1 receptor antagonist
Ppa, pulmonary artery pressure
PVR, pulmonary vascular resistance
Pwp, pulmonary wedge pressure
Pra, right atrial pressure
SV, stroke volume
Psa, systemic arterial blood pressure
SVR, systemic vascular resistance
TNF-α, tumor necrosis factor-α

IL-1 is a cytokine thought to occupy a proximal position in the inflammatory cascade leading to tissue injury during sepsis (1, 2). After its release, IL-1 influences the metabolism of arachidonic acid and results in increased synthesis of leukotrienes, prostaglandins, and thromboxane A_2 (2). In addition, IL-1 acts synergistically with other cytokines, such as TNFα, to potentiate the inflammatory response (3).

Investigators have focused on the role of IL-1 as a prominent mediator of septic shock (3–6) and, in fact, have demonstrated that systemic administration of IL-1 to experimental animals resulted in arterial hypotension (3, 7). These experimental findings are consistent with clinical observations associating septic shock with elevation in IL-1 levels, specifically in patients with Gram-negative bacteremia (8, 9) and in humans receiving endotoxin (10). Furthermore, sepsis-induced arterial hypotension and mortality have been positively modified in *Escherichia coli*-infected adult animals by infusion of an IL-1ra (4, 6).

Although most studies have evaluated Gram-negative sepsis, recent work reveals that Gram-positive bacteria may also induce *in vitro* synthesis and release of IL-1 (11, 12). The data of Sullivan *et al.* (13) showed an early, transient elevation of serum IL-1 levels in a group of children who were infected with *Staphylococcus aureus, Staphylococcus epidermidis*, and

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enterococci, and who eventually died (13). However, the role and hemodynamic consequences of IL-1 in Gram-positive sepsis in the neonatal animal is as yet undefined.

We hypothesized that if IL-1 is an important mediator of sepsis, its blockade in the piglet infected with group B β-hemolytic streptococci would in part ameliorate many of the deleterious hemodynamic consequences of sepsis and improve length of survival. To evaluate this, we used human recombinant IL-1 receptor antagonist and studied its effect when given after GBS sepsis had been initiated in the neonatal piglet.

METHODS

Sixteen Yorkshire piglets less than 2 wk old were anesthetized with sodium pentobarbital (30 mg/kg, intraperitoneally) for the surgical procedure. Femoral arteries and veins were cannulated and used for measurement of Psa, infusion of maintenance fluid and bacteria, and blood sampling. The left external jugular vein was cannulated, and the catheter was advanced into the right atrium and used for infusion of IL-1ra (Synergen, Boulder, CO), measurement of Pra, and the injection of ice-cold saline for determination of CO via thermodilution. A 5 Fr Swan-Ganz thermodilution catheter was placed into the left external jugular vein and advanced under fluoroscopy into the left pulmonary artery to measure Ppa, Pwp, and CO. Heparinized normal saline (10 U/ml) was infused continuously through the pulmonary artery catheter. A 5% dextrose solution was administered via a peripheral vein at a rate of 6 mL/kg/h. Vascular pressures were measured with pressure transducers (model P23–1D; Gould Instruments, Cleveland, OH) and recorded on a multichannel recorder (model 7 polygraph, Grass Instrument, Quincy, MA).

A tracheostomy was performed and a 4–5-mm endotracheal tube inserted. Animals were ventilated with room air using a time-cycled, pressure-limited, infant ventilator (Bournes BP 200, Riverside, CA). Acceptable arterial blood gases were obtained by setting peak inspiratory pressure at 11 cm H_2O, positive end-expiratory pressure at 2 cm H_2O, and the respiratory rate at 35 breaths/min. Ventilator settings were not altered during the study period. Animals were paralyzed with pancuronium bromide using an initial dose of 0.2 mg/kg, i.v., followed by an infusion of 0.4 mg/kg/h. Chloral hydrate (100 mg/kg) was given via a nasogastric tube shortly after the surgery was completed to sedate the animals through the study period. Rectal temperature was continuously monitored with a thermistor probe (Yellow Springs Instrument Co., Yellow Springs, OH), and skin temperature was maintained at 38.5°C using a servo-controlled radiant warmer.

Group B β-hemolytic streptococci (type Ia/c isolated from an infected neonate cared for in the Neonatal Intensive Care Unit at Jackson Memorial Hospital) were cultured in Todd-Hewitt broth for 18 h at 37°C. The bacteria were collected by centrifugation, washed twice in pyrogen-free saline, and resuspended in a sterile Ringer's lactate solution with 5% dextrose. Bacterial concentration was determined by optical density (420 nm) measurements to be 8.75×10^8 colony-forming units/ml. Sepsis was induced by infusion of bacteria at a rate of 7.5×10^7 colony-forming units/kg/min. The infusion was continued until the animal died or 4 h had elapsed.

Dose response studies were performed using newborn piglets who received a continuous infusion of GBS as described above. We tested doses of IL-1ra ranging from 10 to 40 mg/kg, which based on previous studies (4, 6, 14) would assure the serum ratio of IL-1 to IL-1ra necessary to achieve a physiologic response. The dose used in this study was based on a dosage regimen that resulted in the most stable mean Psa during the infusion of bacteria.

Animals were randomly assigned to a treatment group ($n = 8$; $\bar{X} \pm$ SD; weight, 2756 ± 657 g; age, 9 ± 3 d) which received IL-1ra throughout the study or a control group ($n = 8$; weight, 2916 ± 529 g; age, 9 ± 2 d) which received an infusion of normal saline. Fluids in the control group were adjusted so as to balance the total fluids received in the treatment group. After a 30-min stabilization period, hemodynamic (Ppa, Psa, CO, Pra, Pwp) and arterial blood gas measurements were obtained before any intervention (baseline). A continuous infusion of GBS was then begun. Fifteen minutes after the initial rise in Ppa (15–17) (secondary to the GBS infusion), all measurements and arterial blood gas determinations were repeated. Human recombinant IL-1ra was given as an i.v. bolus of 40 mg/kg via an external jugular vein over 5 min, beginning 15 min after the onset of pulmonary hypertension. After completion of the bolus, a constant infusion of IL-1ra was begun at a rate of 60 μg/kg/min. Measurements were subsequently repeated at 30 and 60 min, and every 30 min in both groups until the animals died or 240 min from the onset of pulmonary hypertension had elapsed. Stroke volume, SVR, and PVR were calculated.

Handling and care of the animals were in accordance with the guidelines of the National Institutes of Health, and this study protocol was approved by the Animal Care Committee of the University of Miami.

Analysis of covariance with repeated measures was utilized to assess the response to treatment from 15 min after initiation of pulmonary hypertension up to and including 120 min for both groups for all variables (Psa, Ppa, Pwp, SV, SVR, PVR, heart rate, CO, pH, $Paco_2$, Pao_2, and base deficit) using the 15-min (GBS baseline) value as the covariance correction. This analysis includes tests between groups without regard to time and time-treatment interaction. In all cases treatment group differences were significant; however, only time-treatment p values were reported. Statistical analyses did not include values after 120 min due to mortality in the control group after this time. Hemodynamic and arterial blood gas data were compared between groups at baseline using two sample t tests. The Mann-Whitney U test was used to compare survival time between groups. All animals were followed until death or until 240 min had elapsed. Data are expressed as mean ± SD.

RESULTS

Age and weight were not significantly different between treatment and control animals. In addition, hemodynamic and arterial blood gas measurements at baseline and just before infusion of either IL-1ra or saline were comparable between

groups. Initially, mean Psa increased in both groups after the bacterial infusion was begun (Fig. 1). Mean Psa values remained stable in both groups during the initial 60 min of bacterial infusion, while over the subsequent 60 min, mean Psa in the control group fell steadily to a value of 9 ± 3.5 kPa at 120 min. In contrast, mean Psa in the IL-1ra treatment group remained essentially unchanged at 12.7 ± 2.5 kPa. These differences were statistically significant over time (time-treatment interaction, $p < 0.001$).

Cardiac output initially decreased with GBS infusion in both groups (Fig. 2). However, the IL-1ra treatment group maintained a more stable CO (0.21 ± 0.07 L/min/kg at 120 min) compared with the control group in which CO decreased steadily to 0.13 ± 0.08 L/min/kg (time-treatment interaction, $p < 0.001$).

Stroke volume fell in both groups (Fig. 2). The IL-1ra treatment group maintained a stroke volume ranging from 1.94 ± 0.68 to 1.82 ± 0.65 mL/kg/beat over the 60–120-min period, whereas values in the control group fell from 1.92 ± 0.52 to 1.34 ± 0.62 mL/kg/beat (time-treatment interaction $p < 0.01$). Heart rate was not statistically different between groups (Table 1).

Both groups displayed significant increases in PVR and Pwp with GBS infusion (Fig. 3). Comparison of values over the study period revealed that values in the treatment group were significantly lower than that of the treatment group for both parameters (time-treatment interaction, $p < 0.04$).

There were no statistically significant differences between groups for SVR or mean Ppa (Table 1). In addition, values for arterial blood gases and acid-base status between groups were not statistically different over the study period. pH values at the 15-min GBS baseline were 7.34 ± 0.03 and 7.43 ± 0.06 and at 120 min 7.08 ± 0.09 and 7.24 ± 0.17 in control and IL-1ra groups, respectively. $Paco_2$ values were 4.8 ± 0.7 and 4.4 ± 0.5, and 6.4 ± 1.3 and 5.7 ± 0.9 kPa at 15 and 120 min in control and treatment groups, respectively. PaO_2 values were also not significantly different and were 7.7 ± 2.1 and 6.9 ± 0.7 kPa at 120 min in control and treated animals, respectively.

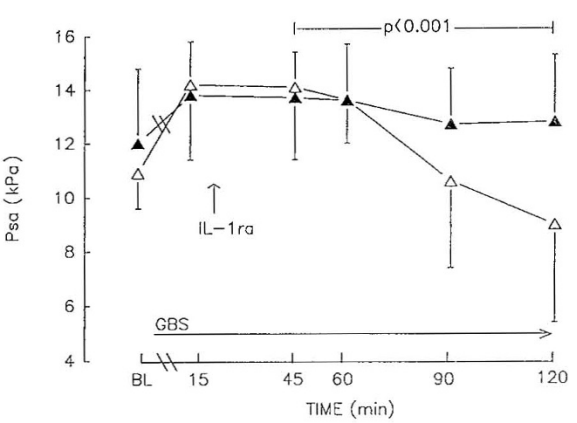

Figure 1. Arterial blood pressure changes in control (△) ($n = 8$) and IL-1ra (▲) ($n = 8$) animals receiving GBS infusion. IL-1ra animals displayed a significantly higher mean arterial blood pressure over time ($p < 0.001$). Values represent $\bar{X}$ ± SD. The *p*value represents time-treatment interaction by repeated measures analysis of covariance. *BL*, baseline.

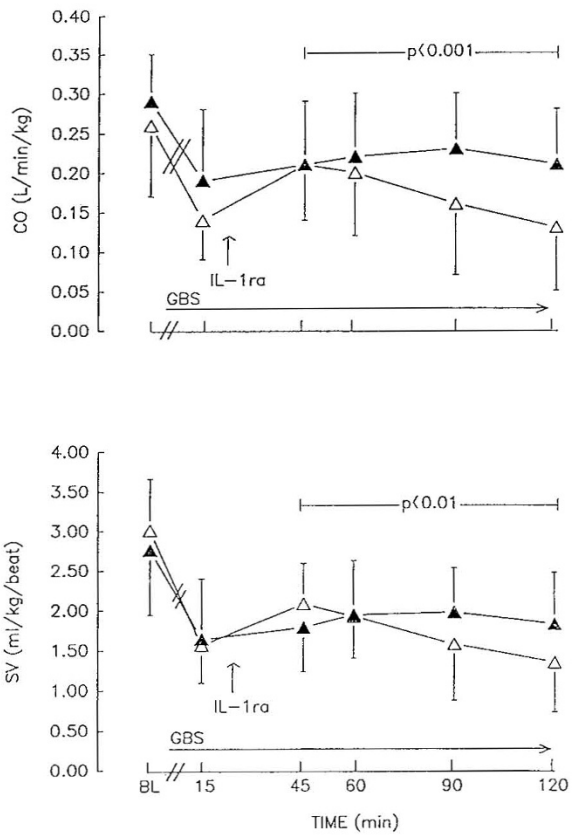

Figure 2. Control animals (△) ($n = 8$) are compared to IL-1ra ($n = 8$) animals (▲) with respect to cardiac output in the upper graph and stroke volume in the lower graph. IL-1ra animals display a significantly higher CO ($p < 0.001$) and SV ($p < 0.01$) over time. *BL*, baseline.

Median survival in the control group was 150 min (range, 120–191 min) and 226 min (range, 155–243 min) in the IL-1ra-treated group ($p = 0.04$).

DISCUSSION

The results of this study affirm previous findings implicating IL-1 as an important mediator of the myocardial dysfunction and hypotension accompanying bacterial sepsis (3, 7). In this study, animals treated with IL-1ra demonstrated a more stable mean Psa and CO when compared with control animals during bacterial infusion. Unfortunately, the study design did not allow definition of the mechanism explaining these findings; however, it is probable that the effect of IL-1 on the cardiovascular system is multifaceted, manifesting direct vascular as well as myocardial effects. Trinkle *et al.* (18), using a vascular smooth muscle preparation, demonstrated that IL-1 depressed smooth muscle contraction by decreasing the concentration of activator calcium required for myosin light chain kinase phosphorylation. In addition, they described alteration in smooth muscle actin expression in those muscle preparations exposed to IL-1. Beasley (19) provided evidence that IL-1 induced elevations in c-GMP which may result in decreased concentration of activator calcium. Furthermore, Finkle *et al.* (20) have recently suggested that cytokines may have a direct negative inotropic effect mediated through myocardial nitric oxide synthase. It is possible that, in our experiment, blockade

Table 1. *Hemodynamic variables*

		$\bar{X}$ ± SD					
	Group	Baseline	15 min	45 min	60 min	90 min	120 min
HR (beats/min)	Control	239 ± 36	298 ± 30	283 ± 40	289 ± 37	281 ± 40	300 ± 25
	IL-1ra	285 ± 28	300 ± 20	315 ± 28	313 ± 44	323 ± 45	330 ± 32
Ppa (kPa)	Control	1.9 ± 0.4	5.5 ± 1.2	5.1 ± 1.2	4.9 ± 1.1	4.7 ± 0.9	4.7 ± 0.9
	IL-1ra	1.7 ± 0.3	5.9 ± 0.8	5.3 ± 0.5	5.2 ± 0.4	4.7 ± 1.1	4.8 ± 0.7
Pra (kPa)	Control	0.33 ± 0.13	0.40 ± 0.30	0.5 ± 0.40	0.40 ± 0.30	0.40 ± 0.30	0.30 ± 0.13
	IL-1ra	0.30 ± 0.13	0.40 ± 0.13	0.5 ± 0.13	0.40 ± 0.30	0.40 ± 0.13	0.40 ± 0.30
SVR (kPa/L/kg/min)	Control	56 ± 31	94 ± 28	70 ± 21	73 ± 24	78 ± 33	87 ± 55
	IL-1ra	44 ± 18	92 ± 49	76 ± 40	68 ± 34	64 ± 30	68 ± 34

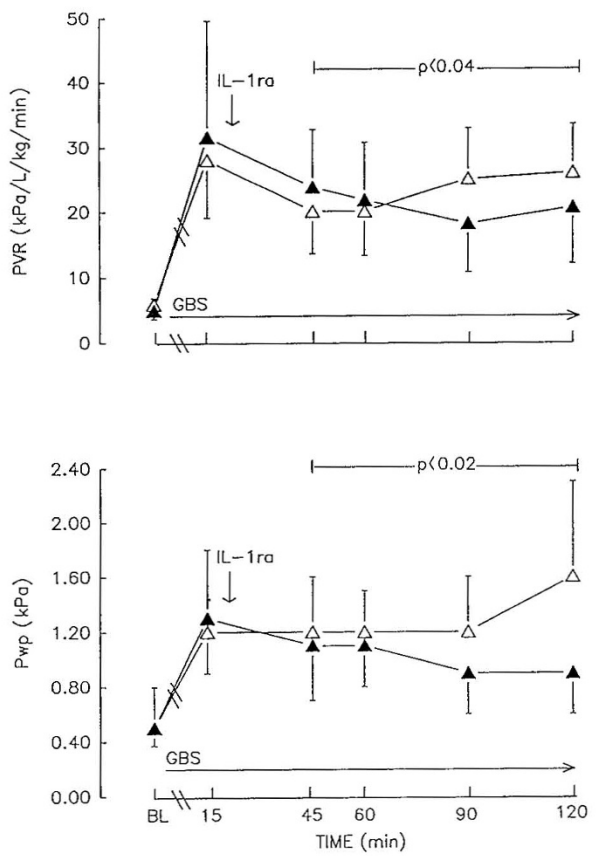

Figure 3. Control animals (△) (n = 8) are compared to IL-1ra (n = 8) animals (▲) with respect to PVR represented in the upper and Pwp in the lower graph. IL-1ra animals display a significantly lower PVR ($p < 0.04$) and Pwp compared to control animals ($p < 0.02$) over time. *BL*, baseline.

of IL-1 receptor sites by IL-1ra served to protect these myocytes from the deleterious direct effects of IL-1 and hence directly improved myocardial function.

Interleukin-1 also interferes with the coupling of β-agonist-occupied receptors with adenylate cyclase, thus altering cardiomyocyte contractility. These data suggest that IL-1 may modulate the hormonal responsiveness and function of the cardiomyocyte (21). In our study, CO and SV, but not SVR or heart rate, were significantly different between the treatment and control groups, implying that the major differences between the groups may be due to differences in cardiac function, not vascular tone. We were not able to demonstrate a direct IL-1 effect because ventricular ejection fraction was not measured. Therefore, although *in vitro* evidence of direct IL-1 activity on the myocardium exists (21), it is also possible that the improved cardiac output observed in the treatment animals was secondary to decreased right ventricular afterload as suggested by the significant fall in PVR.

The improvement in mortality in this study, as in others (6, 22), was most likely due to improved hemodynamic function as well as modulation of the inflammatory response secondary to a decrease in cytokine production. IL-1, -6, and -8 (23–26), as well as TNF-α, are also reduced during IL-1ra administration (27), findings that may also account for the improvement in cardiac output and blood pressure in this model. As measurement of these cytokines was beyond the scope of this study, we cannot therefore assume that the improvement in survival and hemodynamic functions were solely related to IL-1 blockade.

Human recombinant IL-1ra was used in this study because the interspecies homology of IL-1ra is high. Compared with human IL-1ra, for example, murine IL-1ra is 75–77% identical (28). We assumed that human recombinant IL-1ra would be effective in our septic piglet model as it has been used successfully in studies utilizing a variety of mammalian models (4, 6, 29, 30).

The IL-1ra dose chosen in the present investigation is high when compared with other reports. Wakabayashi *et al.* (4) used a pre-bacteremia bolus dose of 10 mg/kg of IL-1ra followed by a constant infusion of 15 μg/kg/min to achieve a significant biologic response. In contrast, we were unable to demonstrate a significant response at these dosages during our preliminary dose-response studies. This may reflect an interspecies difference in response to IL-1ra infusion, the dose and type of bacteria used or, more likely, the fact that the present work tested IL-1ra in a treatment, as opposed to pretreatment model. IL-1 transcription occurs within 15 min in stimulated cells (31), whereas in *in vivo* studies translation and synthesis result in peak serum levels within 2–3 h post-bacterial challenge (32, 33). It is possible that during IL-1ra pretreatment many IL-1 receptor sites are occupied before bacterial stimulation of IL-1 transcription. This could conceivably result in a relative down-regulation of the positive feedback effect that IL-1 typically produces after its synthesis by stimulation of transcription and translation, resulting in additional IL-1 (34). In the present study, it is possible that higher doses of IL-1ra were required in order to overcome the effect of an already ongoing, unchecked positive feedback loop.

In summary, these data suggest that IL-1 plays an important role in mediating the hemodynamic manifestations of GBS sepsis. Specifically, treatment with IL-1 receptor antagonist ameliorates the decrease in cardiac output and mean arterial pressure as well as increases the length of survival in an acute, highly lethal model of neonatal GBS sepsis and septic shock.

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