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Effects of the Thromboxane Synthetase Inhibitor, Dazmegrel (UK 38,485), on Pulmonary Gas Exchange and Hemodynamics in Neonatal Sepsis

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ABSTRACT. Group B streptococcal (GBS) sepsis produces arterial hypoxemia in newborns. In piglets we previously found that hypoxemia develops because of increased ventilation perfusion heterogeneity, and reduced mixed venous pO_2 occurring in association with decreased pulmonary blood flow. We hypothesize that increased thromboxane A_2 (TxA_2) synthesis mediates the immediate alterations in gas exchange found in GBS sepsis. We studied 18 anesthetized, ventilated piglets before, during, and after a 30-min infusion of 2×10^9 colony forming units/kg of GBS. Nine piglets were pretreated with 8 mg/kg of dazmegrel (DAZ), a TxA_2 synthetase inhibitor, and nine animals received GBS without DAZ pretreatment. Pulmonary and systemic arterial pressures, pulmonary vascular resistance, pulmonary blood flow, respiratory gas tensions, intrapulmonary shunt, and SD of pulmonary blood flow, an index of ventilation perfusion mismatching, were measured. Systemic and pulmonary arterial levels of thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ were also measured. The sham-treated animals showed the expected rise in pulmonary arterial pressure from 12 ± 3 to 29 ± 7 torr, ($p < 0.02$). By comparison, the animals pretreated with DAZ did not demonstrate pulmonary arterial hypertension and had a delay in the fall in pulmonary blood flow until 2 h postinfusion. Arterial PO_2 did not decline significantly after the GBS infusion in the DAZ-pretreated animals; the untreated animals showed a significant fall in pO_2 from baseline. There was no significant change in intrapulmonary shunt or SD of pulmonary blood flow compared to baseline in the DAZ-pretreated animals. The elevation in thromboxane B_2 occurring with GBS sepsis did not occur in the DAZ-pretreated animals. We conclude that TxA_2 in part mediates the immediate gas exchange and pulmonary hemodynamic abnormalities during GBS sepsis. Inhibition of TxA_2 synthetase results in preservation of normal pulmonary gas exchange and a delay in the fall in $\dot{Q}_p$ following GBS infusion. (*Pediatr Res* 20: 481–486, 1986)

Abbreviations

GBS, group B streptococci
$\dot{Q}s$, systemic blood flow
$\dot{Q}p$, pulmonary blood flow
$\dot{V}_A/\dot{Q}$, ventilation perfusion
TxA_2, thromboxane A_2
$SD\dot{Q}_p$, SD of pulmonary blood flow
TxB_2, thromboxane B_2
PGI_2, prostacyclin
RIA, radioimmunoassay
PGE_1, prostaglandin E_1
$PGF_{1\alpha}$, prostaglandin $F_{1\alpha}$
PGE_2, prostaglandin E_2
DAZ, dazmegrel

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Hypoxemia develops during an intravenous infusion of GBS in experimental animals (1, 2), indicating a direct or indirect alteration in pulmonary gas exchange as a result of the bacterial sepsis. Mechanisms that might contribute to hypoxemia under these conditions include a reduction in mixed venous pO_2 associated with reduced $\dot{Q}s$, assuming unchanging tissue oxygen extraction and the presence of some degree of ventilation-perfusion mismatching, or an alteration in the distribution of $\dot{Q}_p$. Altered distribution of $\dot{Q}_p$ may result in substantial perfusion of lung areas receiving no ventilation (shunt), or lung areas receiving little ventilation, *i.e.* areas with low $\dot{V}_A/\dot{Q}$ ratios. Both can contribute to hypoxemia depending on extent of diversion of $\dot{Q}_p$ to these areas. We have shown previously in a neonatal piglet model of GBS sepsis that hypoxemia develops because of both reduced $\dot{Q}_p$ and mismatching of alveolar $\dot{V}_A/\dot{Q}$ producing an increase in flow to poorly ventilated lung regions, without a significant increase in intrapulmonary shunt (2).

Others have demonstrated that the vasoconstrictor prostaglandin metabolite, TxA_2, mediates the rise in pulmonary arterial pressure, which also occurs during the initial phase of GBS sepsis (1, 3). Piglets treated with the cyclooxygenase inhibitor, indomethacin, have not shown GBS-induced pulmonary hypertension (1). Based on these findings, the present study was designed to test the possibility that blocking the rise in pulmonary arterial pressure with a specific inhibitor of thromboxane synthetase would also inhibit the development of hypoxemia in a septic newborn piglet by preventing the fall in $\dot{Q}_p$ and the development of $\dot{V}_A/\dot{Q}$ mismatching.

METHODS

Animal preparation. Eighteen piglets, age 10 to 16 days, were obtained and prepared as previously described (2). The animals were anesthetized with pentobarbital, 25 mg/kg intravenously, initially, then 5 mg/kg/h. They were paralyzed with pancuronium (0.1 mg/kg/dose prn), tracheostomized, and mechanically ventilated with a tidal volume of 12 to 15 ml/kg with a small animal fixed volume ventilator (Harvard Apparatus, Millis, MA). Systemic arterial and pulmonary arterial catheters were placed for pressure monitoring and blood sampling. Two peripheral

venous catheters were placed, one for infusion of inert gas solution, the other for infusion of live GBS. Rectal temperature was monitored continuously and maintained at 38 ± 0.5° C.

Minute ventilation was calculated by multiplying the tidal volume, as measured by the hot wire anomometer (4) placed in the expired gas stream, by the frequency of ventilator breaths. Total $\dot{Q}_p$ was determined by the thermodilution technique (Edwards 510 C.O. computer) using 2-ml samples of 5% dextrose in water at 0° C with measurements made in triplicate or quadruplicate if a greater that 10% discrepancy occurred in the first three samplings (5). Stroke volume was calculated by dividing $\dot{Q}_p$ by heart rate. An index of pulmonary vascular resistance was calculated according to the formula $PVR = (P_{pa} - P_{cwp})/\dot{Q}_p$ where P_{pa} = mean pulmonary arterial pressure, P_{cwp} = mean pulmonary capillary wedge pressure, and $\dot{Q}_p$ = total pulmonary blood flow. An index of systemic vascular resistance was calculated by dividing mean systemic arterial pressure by $\dot{Q}_p$, assuming $\dot{Q}_s = \dot{Q}_p$.

Arterial and mixed venous blood gas tensions and pH were measured within 3 min of blood sampling on a Corning 165 blood gas analyzer. Results were corrected to the animal's temperature.

Assessment of ventilation perfusion matching. The multiple inert gas elimination technique (6) was employed to assess intrapulmonary shunt and distribution of $\dot{V}_A/\dot{Q}$ ratios. This technique has been modified, as previously described, for use in small animals (7, 8). Data derived from the analysis of each of the six inert gases in the pulmonary and systemic arterial blood and mixed expired gases included intrapulmonary shunt and $SD\dot{Q}_p$. The latter is a unitless index of overall ventilation-perfusion heterogeneity, separate from shunt and dead space (9, 10).

Bacterial preparation. Group B β-hemolytic streptococci (type III) were inoculated into Todd Hewitt broth and incubated at 32° C for 18 h prior to each experiment. The broth culture was centrifuged at 4 × *g* at 3° C for 30 min. The bacterial pellet was resuspended in 10 ml phosphate-buffered saline. Bacterial concentration of the resuspended solution was determined by measurement of the optical density with comparison to a previously determined plot of bacterial colony forming units to optical density.

Assessment of prostaglandin metabolites. Four times during the protocol 2-ml blood samples were obtained simultaneously from the systemic arterial and pulmonary arterial circulation. The blood was drawn into an inhibitor solution of 0.6 mg indomethacin and 2 mg of sodium EDTA per ml of blood. The inhibitor solution and the inhibitor-blood mixture were kept in an ice bath until centrifugation at 15,000 rpm for 10 min in a refrigerated centrifuge. The decanted fluid was promptly frozen and stored at −70° C until analysis. Assays for TxB_2, the stable metabolite of TxA_2, and 6-keto-$PGF_{1\alpha}$, the stable metabolite of prostacyclin, were measured by Dr. John Harlan, Department of Medicine, University of Washington, Seattle, WA. The RIA for TxB_2 used a commercially available kit (New England Nuclear, Boston, MA). The level of sensitivity was 10 pg/100 μl of sample. The RIA for 6-keto-$PGF_{1\alpha}$ used a locally prepared antibody; sensitivity level was 10 pg /300 μl of sample. Cross-reactivity of the 6-keto-$PGF_{1\alpha}$ antibody at a normalized percent bound of 50% was $PGF_{1\alpha}$, < 7.8%; PGE_1, < 3%; $PGF_{2\alpha}$, < 2.7%; PGE_2, < 2%; prostaglandin A_1, < 0.3%; prostaglandin A_2, < 0.1%; TxB_2, < 0.1%; and 13,14-dihydro-15 keto-$PGF_{2\alpha}$, < 0.02% (New England Nuclear Technical Bulletin HEK-008). Cross-reactivity of the TxB_2 antibody at normalized bound of 50% was PGE_2 < 0.2%, PGA_2 < 0.2%, PGF_2 < 0.2%, and 6-keto-$PGF_{1\alpha}$ < 0.2% (New England Nuclear Technical Bulletin NEK-007) (11, 12). The TxB_2 and 6-keto-$PGF_{1\alpha}$ levels were determined by direct assay of anesthetized piglet plasma. Matrix effects due to protein present in unknown piglet plasma samples were determined in standard curves run in eicosnoid free piglet plasma prepared as previously described (12). Samples were analyzed in duplicate and the values for the 6-keto-$PGF_{1\alpha}$ and TxB_2 are expressed as the average of the two values obtained with each analysis.

Experimental protocol. Figure 1 depicts the experimental protocol. Following collection of a baseline set of data, the animals were randomized to receive 8 mg/kg DAZ (UK 38, 485, kindly supplied by Dr. R. Urguilla, Pfizer Laboratories, Groton, CT) or the carrier solution for DAZ. The powder form of DAZ was dissolved in 1 ml 0.1 N NaOH to which 0.9% saline was added to make 5 ml of solution. This mixture was infused in each of the treated animals over a 5-min period. Sham-treated animals received the same NaOH-saline solution without the DAZ.

Thirty minutes following the drug treatment, a second set of samples was obtained to determine any hemodynamic effects of the DAZ in the piglets. Following these measurements, an infusion of 2×10^9 colony forming units/kg of GBS was administered over 30 min. Twenty minutes into the infusion of bacteria, a third set of samples was obtained. Finally, at 1 h (and 2 h in the DAZ-treated group) sample 4 (and 5) were obtained. Measurement of $\dot{Q}_p$, P_{pa}, PVR, respiratory gas tensions, pH, and systemic arterial pressure was made each of the sampling periods. Analysis of prostaglandin metabolites was performed for sampling periods 1 through 4. Inert gas data were obtained at sampling times 1 through 5 in the DAZ pretreated animals but not the control animals. Inert gas data from a previously studied set of control animals (2) are shown for comparison with the results obtained from the DAZ-pretreated animals.

Statistics. One-way analysis of variance was carried out to ascertain possible statistical significance within groups. If this

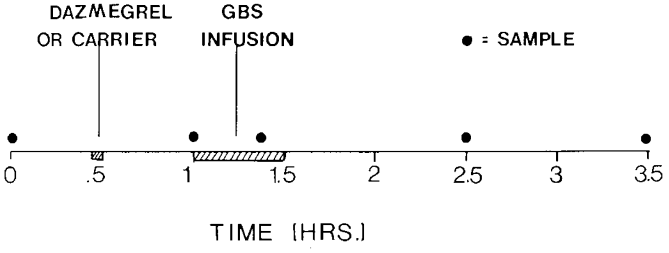

Fig. 1. The protocol for the experiment plotted as time against the various manipulations is illustrated. The *solid circles* represent the sampling points at which hemodynamic and gas exchange measurements were obtained. Note that the third sampling time occurred near the end of the bacterial infusion. See text for details.

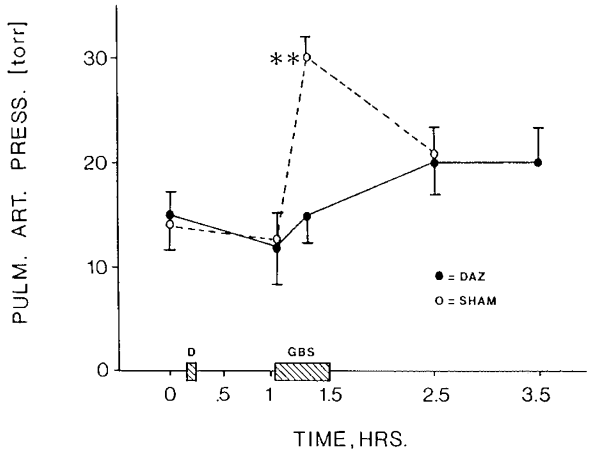

Fig. 2. The change in pulmonary arterial pressure is plotted for the sham-treated and DAZ-treated groups of animals. The "*D*" by the *short hatched area* on the *abscissa* indicates the 5 min infusion of either DAZ or the carrier without the drug (sham). The "*GBS*" by the *longer hatched area* indicates the 30-min bacterial infusion. There is a significant rise in pulmonary arterial pressure in the sham-treated animals ($p < 0.02$) during the infusion, compared to baseline value. There is no significant change in mean pulmonary arterial pressure in the DAZ-pretreated animals compared to baseline. ** = $p < 0.02$.

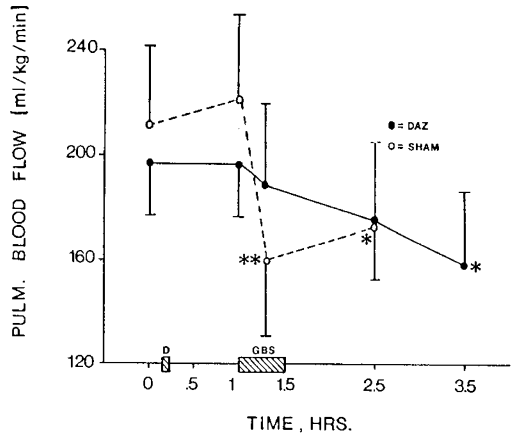

Fig. 3. Total pulmonary blood flow ($\dot{Q}_p$) in ml/kg/min against time in hours. There is a reduction in $\dot{Q}_p$ in the sham-treated animals 20 min into the bacterial infusion ($p < 0.02$) and 1 h following the end of the infusion compared to baseline. The DAZ-pretreated animals demonstrated a significant fall in $\dot{Q}_p$ only at 2 h following the end of the bacterial infusion ($p < 0.02$) compared to baseline. ** = $p < 0.02$.

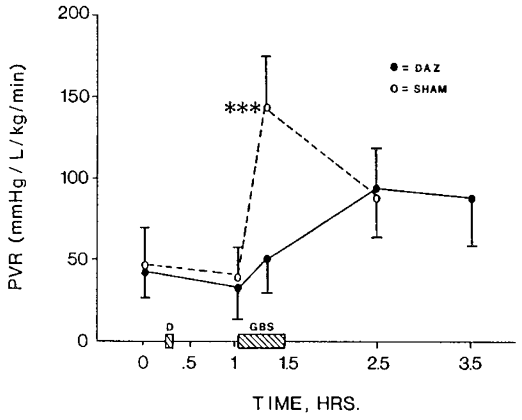

Fig. 4. Plots calculated pulmonary vascular resistance (in units of mm Hg/liter/min/kg) against time. The sham-treated animals showed a significant increase ($p < 0.001$) compared to baseline conditions in PVR 20 min into the bacterial infusion. At 1 h postinfusion the animals returned toward baseline. There was an insignificant rise in the PVR compared to baseline for the DAZ-treated animals. *** = $p < 0.001$.

maneuver indicated statistical significance, then the paired t test was used for intragroup comparisons and the unpaired t test was used for intergroup comparisons. A p value of <0.02 was considered significant to minimize the effects of multiple comparisons of the paired data with baseline measurements, when the baseline measurement was compared to three postbaseline sampling points. The nonparametric Mann Whitney U test was used for analysis of inert gas data (13).

RESULTS

The two groups of piglets were well matched for weight at the time of study (DAZ = 3.1 ± 0.5 kg and control = 3.2 ± 0.6 kg) and did not differ significantly in any of the baseline measurements. All animals were free of bacterial sepsis at the start of the experiment, based on blood cultures obtained at that time.

Figure 2 illustrates the changes in pulmonary arterial pressure between the two groups. DAZ administration had no effect on pulmonary arterial pressure prior to the onset of the GBS infusion. The rise in P_{pa} previously reported in experimental GBS sepsis occurred in the sham treated group but was blunted in the

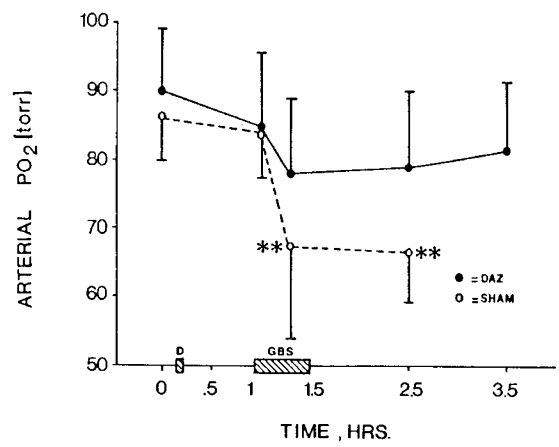

Fig. 5. Plots arterial oxygen tension against time. The sham-treated animals showed a significant fall in the arterial PO_2 ($p < 0.02$) at 20 min and at 1 h postinfusion. In contrast, the DAZ-pretreated animals sustained no significant fall in arterial pO_2 compared to baseline. ** = $p < 0.02$.

DAZ-treated group, never showing a statistically significant rise from baseline during the duration of the observations.

Figure 3 depicts changes in $\dot{Q}_p$. A significant fall with the sham treated group occurred at 20 min after the infusion reconfirming previous observations (1, 2). There was no change in $\dot{Q}_p$ in the DAZ treated group at 20 min, but by 2 h after the end of the bacterial infusion, $\dot{Q}_p$ had fallen equally in the DAZ-treated and control groups.

Figure 4 illustrates the calculated pulmonary vascular resistance. The immediate large increase in PVR at 20 min in the sham-treated group did not occur in the DAZ-treated group. However, by 1 h following the end of the GBS infusion, PVR in both groups was not significantly different, as there had been a small rise in PVR in the DAZ-treated group.

Figure 5 illustrates changes in arterial oxygen tension during the experiment. The DAZ-treated group did not show a significant fall from baseline in arterial oxygen tension during or following the bacterial infusion. In contrast, the arterial pO_2 declined ($p < 0.02$) from the mean baseline value during the infusion of GBS, and remained depressed thereafter.

Figures 6*A* and *B* demonstrate the effects of DAZ on inert gas exchange in septic piglets. There was no significant change, compared to baseline data, in intrapulmonary shunt, or in the magnitude of the low $\dot{V}_A/\dot{Q}$ areas during GBS infusion in the animals pretreated with DAZ. Previously reported results for $SD\dot{Q}_P$ (2) in non-DAZ treated animals showed a significant increase in $SD\dot{Q}_P$. These data are shown for comparison in Figures 6*A* and *B*.

Figures 7*A* and *B* illustrate the results of the prostaglandin metabolite measurements in plasma sampled from the systemic artery. Figure 7*A* demonstrates the significant rise in arterial TxB_2 levels during and following GBS infusion in the sham pretreated animals. There was no rise in TxB_2 with the DAZ-pretreated animals. Figure 7*B* illustrates a small, statistically insignificant increase in 6-keto-$PGF_{1\alpha}$ in the DAZ-treated group. In the sham-treated group, there was also no significant rise. For both TxB_2 and 6-keto-$PGF_{1\alpha}$, the systemic arterial values were approximately 20% higher in all cases than the values obtained from plasma drawn from the pulmonary artery.

Figure 8 illustrates the significant correlation between TxB_2 and calculated pulmonary vascular resistance for all animals at any point during the experiment.

Table 1 shows values for mean systemic arterial pressure, systemic vascular resistance, calculated stroke volume, and heart rate. The immediate rise in systemic vascular resistance with GBS infusion found in the sham-treated group was delayed in the DAZ-treated group. The immediate decline in stroke volume

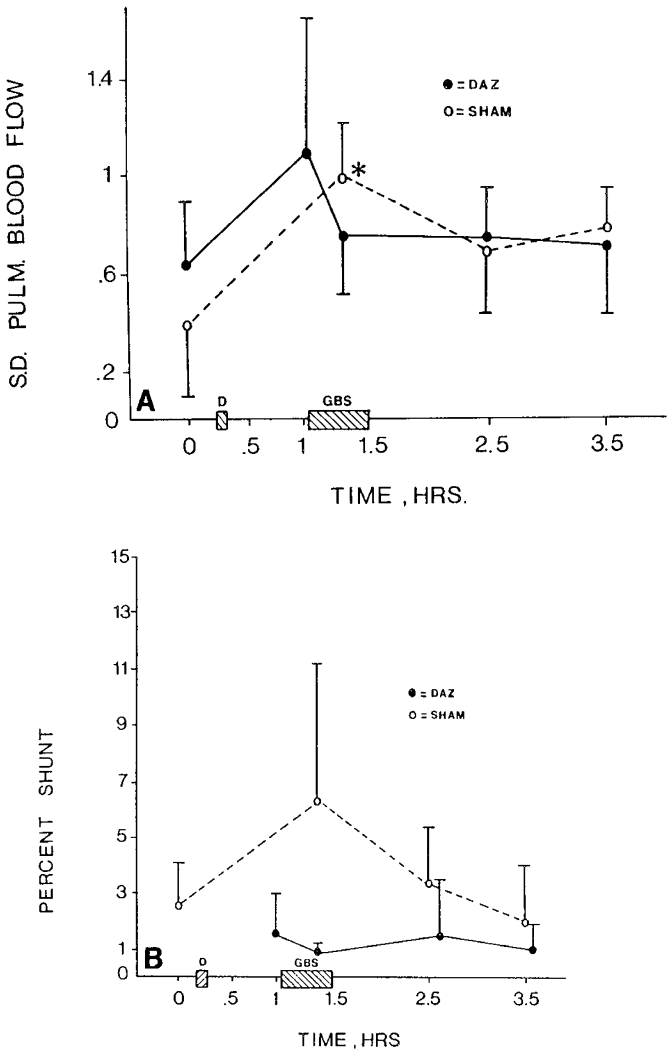

Fig. 6.*A*, a plot of the unitless index of the $SD\dot{Q}_p$ against time. Results from untreated animals (2) are shown for comparison, and as previously reported, demonstrate a significant increase in the index of $\dot{V}_A/\dot{Q}$ heterogeneity at 20 min into the bacterial infusion. In contrast, the DAZ-pretreated animals had no significant change compared to their single baseline movement. * = $p < 0.05$. *B* shows the plot of intrapulmonary shunt versus time. As previously reported (2) untreated animals demonstrated an insignificant rise in mean intrapulmonary shunt measured by the multiple inert gas elimination technique (see text for details). The DAZ-pretreated animals also showed no change in intrapulmonary shunt during the experiment.

with GBS infusion was delayed until 2 h post-GBS infusion in the DAZ-treated group.

Neither mixed venous oxygen tension nor pulmonary capillary wedge pressure was significantly different from baseline at any experimental point in the two groups.

DISCUSSION

The results of this study demonstrate that pretreatment of neonatal piglets with DAZ, a thromboxane synthetase inhibitor, blocks the immediate rise in P_{pa}, blunts the decline in PaO_2, and delays the decline in $\dot{Q}_p$, stroke volume, and the rise in SVR which accompany the intravenous infusion of GBS. Pulmonary gas exchange abnormalities, noted in previously studied septic piglets using the inert gas elimination technique (2), were inhibited by pretreatment with DAZ. Finally, this study demonstrates that DAZ blocks the expected rise in circulating levels of TxB_2, the stable metabolite of the vasoconstrictor substance TxA_2.

Others have also utilized substances known to block pathways of prostaglandin metabolism in order to study changes occurring with acute bacterial infusion. Rojas *et al.* (3, 14) utilized the cyclooxygenase blocker indomethacin and demonstrated an inhibition in the acute rise in P_{pa} occurring with infusion of GBS in adult sheep, an effect that was not blocked by the corticosteroid

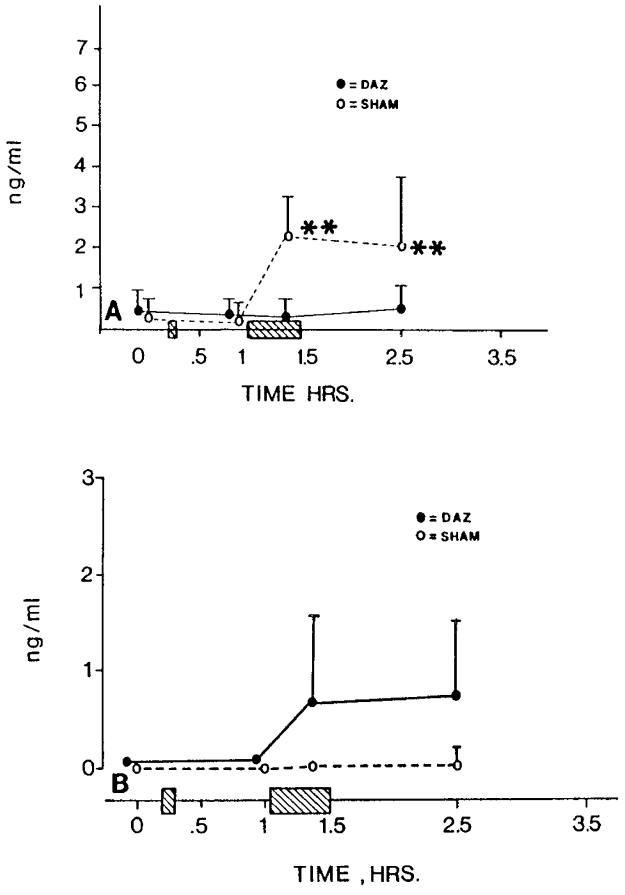

Fig. 7.*A*, plots levels of TxB_2 expressed in ng/ml. Sham-treated animals showed a rise in TxB_2 levels from baseline conditions at 20 min into the infusion of bacteria and at 1 h following infusion ($p < 0.02$). There was no significant change in the mean levels in the DAZ-pretreated animals. ** = $p < 0.02$. *B* illustrates 6-keto-$PGF_{1\alpha}$ levels expressed in ng/ml. No significant rise was detected in the sham or DAZ-treated animals.

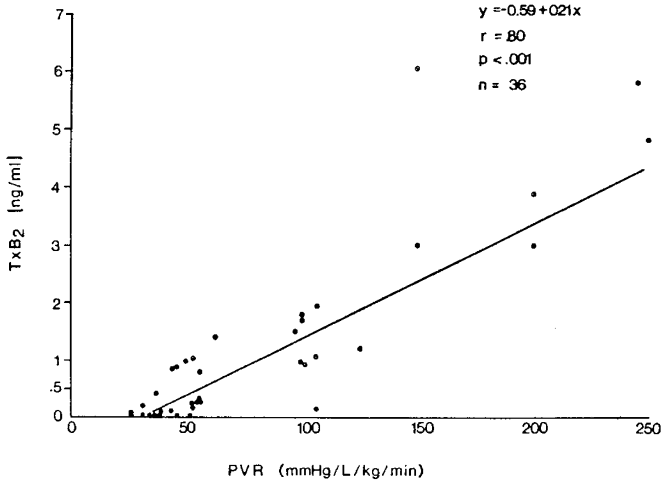

Fig. 8. Plots the level of TxB_2 against calculated pulmonary vascular resistance. There is a significant correlation ($R = 0.8$, $p < 0.001$) for 36 determinations in which TxB_2 was assessed at the same time as pulmonary vascular resistance.

Table 1. *Hemodynamic data*

	Sham treated (condition)				DAZ treated (condition)				
	Baseline	Postinfusion of carrier	During GBS infusion	1 h after GBS infusion	Baseline	Postinfusion of DAZ	During GBS infusion	1 h after GBS infusion	2 h after GBS infusion
HR* (beats/m)	177 ± 25	193 ± 40	188 ± 26	190 ± 34	190 ± 37	194 ± 40	194 ± 29	225 ± 41	236 ± 41
SV (ml/beat)	3.7 ± 0.6	4.0 ± 1.1	2.9 ± 0.9†	3.2 ± 1.0	3.5 ± 1.0	3.5 ± 1.1	3.2 ± 0.9	2.4 ± 1.0	2.1 ± 1.2‡
SVR (mm Hg/liter/min/kg)	381 ± 95	394 ± 115	584 ± 193†	477 ± 125	377 ± 69	341 ± 52	376 ± 75	490 ± 85	545 ± 152†
P systemic (mm Hg)	80 ± 8	83 ± 14	90 ± 9	86 ± 186	80 ± 6	76 ± 9	79 ± 16	86 ± 16	81 ± 20

* HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; P systemic, systemic mean arterial pressure.
† $p < 0.05$.
‡ $p < 0.02$.

methylprednisolone. However, there was no inhibition of increased lung lymph flow, detectable beginning several hours after GBS infusion, suggesting that changes in permeability were not mediated by arachidonic acid metabolites (3). Harlan *et al.* (15), utilizing a different thromboxane synthetase inhibitor, dazoxiben, demonstrated an inhibition in the rise of pulmonary arterial pressure during *Escherichia coli* endotoxin infusion. Winn *et al.* (12) also utilized dazoxiben in a goat model and suppressed the elevation in P_{pa}. However, they demonstrated a greater fall in arterial PO_2 in the animals pretreated with dazoxiben than in untreated animals prior to infusion of the endotoxin. These results (12) raised questions as to the importance of the changes in pulmonary hemodynamics as a regulator of gas exchange. In contrast, Runkle *et al.* (1) demonstrated a restoration of normal pulmonary hemodynamics and arterial oxygen tension with use of the cyclooxygenase inhibitor indomethacin in piglets receiving a continuous infusion of GBS. However, because of the relatively nonspecific effects of indomethacin, which blocks at a proximal point in the pathway leading to TxA_2 synthesis, their results were not directly comparable to the work of Winn *et al.* (12) or the present results. Our work confirms the importance in young animals that TxA_2 helps regulate pulmonary arterial pressure. Our results are consistent with those of Farrukh *et al.* (16) who demonstrated that TxA_2 was the dominant mediator of pulmonary hypertension induced by arachidonic acid or lipid infusion into an isolated lobe preparation.

The present results are the first in neonatal animals to use the substance DAZ. This experimental substance appears to be a more specific blocker of TxA_2 synthesis than dazoxiben (17). Utilizing a specific TxA_2 synthetase inhibitor should minimize the potential increase in synthesis of other prostaglandin metabolites from increased activity of a different pathway when one metabolic pathway is blocked. For example, inhibition of leukotriene synthesis with diethylcarbamazine has been associated with increased production of PGI_2 synthesis (18). Similarly, blockage of the cyclooxygenase pathway may stimulate increased production of leukotrienes, themselves potent vaso- and bronchoconstrictors (19). The findings in our experiment of an insignificant rise in PGI_2 with DAZ pretreatment suggests that there was no or minimal increased production of this metabolite. This result contrasts with the results of Runkle *et al.* (1) in which a more substantial increase in 6-keto-$PGF_{1\alpha}$ was detected. The correlation between TxA_2 and PVR (Fig. 8) supports the thesis that TxA_2 is a major mediator of pulmonary vascular constriction induced by live bacteria or endotoxin.

Our results also demonstrate an association between blocking the acute elevation in PVR and the fall in $\dot{Q}_p$, and regulation of pulmonary gas exchange. Others have found that acute reversal of preexisting pulmonary hypertension may result in impaired gas exchange because of an increase in shunt or low $\dot{V}_A/\dot{Q}$ lung regions (20, 21). The present results are consistent with previous experimental findings that moderate degrees of pulmonary hypertension do not predispose to deterioration of $\dot{V}_A/\dot{Q}$ matching, but more extreme elevations of P_{pa}, at least in newborn animals, may be associated with increased shunt or increased $\dot{V}_A/\dot{Q}$ mismatching (22). The effect of DAZ in preventing a decline in pO_2 may be brief in duration. By 1 h post-GBS infusion, there was no statistical difference in mean arterial pO_2 between the two groups.

The acute fall in stroke volume in the sham-treated animals may have occurred because of the concomitant rise in SVR, or because of decreased myocardial contractility. The delay in the rise in afterload, as measured by SVR, in the DAZ-treated animals suggests that release of TxA_2 may only partially mediate elevations in SVR and other factors also regulate systemic vasoconstriction.

The present results suggest a relationship between alterations in pulmonary arterial pressure and pulmonary gas exchange. We speculate that extreme rises in pulmonary arterial pressure in neonates may inhibit the mechanisms preserving efficient pulmonary gas exchange. To the extent that this disruption contributes to the pathophysiology of early onset GBS sepsis, then DAZ, or similar substances, may play a role in the therapy of this highly lethal disease. This speculation is consistent with results using indomethacin or ibuprofen as a cyclooxygenase inhibitor in a different model of GBS sepsis (23). Further experimental work assessing the effects of DAZ administration at the time of, or even following, the acute effects of GBS infusion will support or refute this speculation.

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Announcement

Amino Acids in Health and Disease

A Searle-UCLA Symposium, organized by Drs. John Fernstrom, Jack Filer, Seymour Kaufman, Robert Roth, Lewis Stegink and Savio Woo will be presented May 30 to June 4, 1986 in Keystone, CO. A multi-disciplinary meeting to examine new research on amino acid transport, metabolism, and function; a heavy emphasis will be placed on amino acids acting on the brain. Major sessions will be held on Amino Acid Transport (chaired by H. Christensen, University of Michigan); Hydroxylases (chaired by S. Kaufman, NIMH); Neurotransmitter Regulation: Behavior and Function: Appetite; Behavior and Function: Blood Pressure; and Disease States: The PKU Paradigm (chaired by S. Woo, Baylor College of Medicine). Informal workshops will be held on Pathophysiology of Amino Acid Transport; Regulation of Hydroxylases; Neurotransmitters and Behavior; and Molecular Genetics. Conference fee: $132; CME credit will be available. *Contact* UCLA Symposia, Molecular Biology Institute, University of California, Los Angeles, CA 90024; (213) 206-6292.