

THE EFFECTS OF IBUPROFEN ON THE PHYSIOLOGY AND SURVIVAL OF PATIENTS WITH SEPSIS

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ABSTRACT

Background In patients with sepsis the production of arachidonic acid metabolites by cyclooxygenase increases, but the pathophysiologic role of these prostaglandins is unclear. In animal models, inhibition of cyclooxygenase by treatment with ibuprofen before the onset of sepsis reduces physiologic abnormalities and improves survival. In pilot studies of patients with sepsis, treatment with ibuprofen led to improvements in gas exchange and airway mechanics.

Methods From October 1989 to March 1995, we conducted a randomized, double-blind, placebo-controlled trial of intravenous ibuprofen (10 mg per kilogram of body weight [maximal dose, 800 mg], given every six hours for eight doses) in 455 patients who had sepsis, defined as fever, tachycardia, tachypnea, and acute failure of at least one organ system.

Results In the ibuprofen group, but not the placebo group, there were significant declines in urinary levels of prostacyclin and thromboxane, temperature, heart rate, oxygen consumption, and lactic acidosis. With ibuprofen therapy there was no increased incidence of renal dysfunction, gastrointestinal bleeding, or other adverse events. However, treatment with ibuprofen did not reduce the incidence or duration of shock or the acute respiratory distress syndrome and did not significantly improve the rate of survival at 30 days (mortality, 37 percent with ibuprofen vs. 40 percent with placebo).

Conclusions In patients with sepsis, treatment with ibuprofen reduces levels of prostacyclin and thromboxane and decreases fever, tachycardia, oxygen consumption, and lactic acidosis, but it does not prevent the development of shock or the acute respiratory distress syndrome and does not improve survival. (N Engl J Med 1997;336:912-8.)

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SEPSIS is associated with a mortality rate of 30 to 50 percent and with substantial morbidity.¹ The relative contributions of the inflammatory response and infection to these adverse outcomes are unknown.^{2,3} In animal models of sepsis, treatment with nonsteroidal antiinflammatory drugs improves survival and reduces physiologic abnormalities.⁴⁻⁸ The synthesis of prostaglandin and thromboxane has been linked with abnormalities of airway mechanics, pulmonary hypertension, hypoxemia, cardiovascular collapse, and multiple organ failure in animals and in humans with the sepsis syndrome.⁹⁻²⁵

Ibuprofen has been shown to have effects on sepsis in humans, but because of their small samples (fewer than 30 patients), previous studies have been inadequate to assess effects on mortality.²⁶⁻²⁸ We sought to determine whether ibuprofen can alter rates of organ failure and mortality in patients with the sepsis syndrome, how the drug affects the increased metabolic demand in sepsis (e.g., fever, tachypnea, tachycardia, hypoxemia, and lactic acidosis), and what potential adverse effects the drug has in the sepsis syndrome.

METHODS

Study Patients

Seven medical centers in the United States and Canada participated in this trial, which was approved by the institutional review board at each center. Consent was obtained from all the patients or their next of kin before enrollment. Patients were recruited from intensive care units if they had a known or suspected site of serious infection, as determined on the basis of clinical data available at the time of screening, and if they met certain criteria that represented a modification of the criteria for sepsis described by Bone et al.²⁹ and that were similar to those defined at a consensus conference.² There were two groups of criteria, one (group 1) involving conditions present when the patient was at rest, and the second (group 2) involving dynamic variables unrelated to coexisting disease. To be eligible for the study, a patient had to meet all the group 1 criteria, as follows: a core temperature of at least 38.3°C or less than 35.5°C, a heart rate of at least 90 beats per minute (in the absence of treatment with beta-blockers), and a respiratory rate of 20 breaths per minute or more or, if the patient was receiving mechanical ventilation, a ventilatory rate greater than 10 liters per minute. In addition, the patient had to meet at least one criterion in group 2, as follows: cardiovascular dysfunction, defined as a systolic blood pressure less than 90 mm Hg or a decrease in systolic pressure by at least 40 mm Hg for more than one

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hour while pulmonary-artery wedge pressures remained adequate (≥ 12 mm Hg) or at least 500 ml of saline was infused; renal-system dysfunction, defined as a urinary output of less than 30 ml per hour or less than 0.5 ml per kilogram of body weight, for at least one hour; dysfunction related to the acute respiratory distress syndrome (ARDS), as defined by a ratio of the partial pressure of arterial oxygen (in millimeters of mercury) to the fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) of less than 200 in the presence of acute, diffuse bilateral infiltrates; pulmonary-system dysfunction, defined as a PaO_2 of less than 70 mm Hg while the patient was breathing room air or a $\text{PaO}_2/\text{FiO}_2$ of less than 333 if the patient was receiving supplemental oxygen (if the patient had pneumonia or chronic lung disease as the solitary cause of sepsis, he or she was also required to meet the definition of ARDS); or central nervous system dysfunction, defined as a decrease in the Glasgow coma score by at least two points.

A maximum of 24 hours was allowed for the patient to meet the entry criteria and for the study drug to be administered. Patients were excluded if they were pregnant, were less than 18 years old, had suspected hypersensitivity to cyclooxygenase inhibitors, had received a cyclooxygenase inhibitor within the preceding 12 hours (or aspirin within the preceding 24 hours), or were enrolled in another experimental study or if consent could not be obtained. We also excluded patients who had suspected brain death, advanced renal failure (serum creatinine, >4 mg per deciliter [$354 \mu\text{mol}$ per liter] unless the patient's condition was stable and the patient was receiving long-term dialysis) or hepatic failure (serum bilirubin, >4 mg per deciliter [$68 \mu\text{mol}$ per liter]), a core temperature of less than 32.2°C , a platelet count of less than 20,000 per cubic millimeter, a granulocyte count of less than 1000 per cubic millimeter due to causes other than sepsis, human immunodeficiency virus infection, gastrointestinal bleeding, or a life expectancy of less than six hours; those who were treated with major immunosuppressive drugs; and those whose physicians were not committed to providing aggressive life support.

Treatment Assignments

Patients were assigned to the study groups in a blinded fashion in each treatment center with the use of a permuted-block randomization algorithm. They received either ibuprofen (Motrin, Upjohn), given intravenously in a dose of 10 mg per kilogram (maximal dose, 800 mg) over a period of 30 to 60 minutes every 6 hours for eight doses or placebo (glycine-buffer vehicle) administered in the same volume and at the same times. Both the patient and the care givers were unaware of the patient's treatment assignment.

Laboratory Data

Before the first dose of the study drug, a base-line medical history was taken and a physical examination was performed to document the presumed cause, site, and time of onset of the sepsis syndrome. Blood was obtained for culture from at least two sites. Infection was classified as occurring in the lungs, peritoneum, or urinary tract or at another site or an unknown site. Chest radiographs were obtained at entry and scored by the chest radiologist to indicate the presence and severity of pulmonary edema.²⁶

The method of calculating the Acute Physiology and Chronic Health Evaluation (APACHE II) score was modified so that the score represented a point in time — that is, it was calculated from the base-line data rather than from the worst values obtained during the first 24 hours of care in the intensive care unit. Data obtained at entry and every 4 hours thereafter for the first 44 hours and then at 72, 96, and 120 hours included the patient's temperature, mean systemic blood pressure, respiratory rate, heart rate, urinary output (as an hourly average), arterial-blood gas measurements, and requirement for antipyretic agents. Values for mean blood pressure were calculated with the following formula: $(0.33 \times \text{systolic pressure}) + (0.67 \times \text{diastolic pressure})$. When a pulmonary-artery catheter was present, the cardiac output, pulmonary-artery pressure, pulmonary-wedge pressure, and central venous

pressure were measured at base line and 20 hours later. Blood lactate was measured, and the delivery and consumption of oxygen calculated, at base line and 20 hours.³⁰

Blood samples were obtained at base line and 20, 44, 72, and 120 hours after study entry for the measurement of hemoglobin, the total leukocyte count, the platelet count, bilirubin, serum aspartate aminotransferase, lactate dehydrogenase, creatinine, blood urea nitrogen, and electrolytes. Data were recorded on the patient's requirements for blood transfusion, intensive care, and mechanical ventilation.

Measurements of Ibuprofen and Eicosanoids

Samples of urine and blood were obtained at base line and 20, 44, 72, 96, and 120 hours after study entry and were maintained at -70°C . Batch assays using stable isotope-dilution methods in conjunction with gas chromatography-mass spectrometry to detect urinary 11-dehydro-thromboxane B_2 and 2,3-dinor 6-keto-prostaglandin- $\text{F}_{1\alpha}$ were performed by the Vanderbilt Prostaglandin Core Laboratory.^{31,32} Ibuprofen levels were measured in plasma samples obtained at base line and 20 hours after study entry.³³

Definitions

We used the entry criteria listed in group 2 above to define shock, ARDS, pulmonary-system dysfunction, and renal dysfunction. Shock was considered to have been reversed when the systolic blood pressure was stable and greater than 90 mm Hg for 12 hours without vasopressor support. Reversal of ARDS was considered to have occurred when the patient no longer met the criteria for ARDS on the basis of either arterial-blood gas measurement or chest radiography, and when the reversal lasted at least 24 hours.

We calculated the number of failure-free days (days without organ-system dysfunction) for the clinically important organ systems, as described above, during the 30 days immediately after study entry. For example, a patient who survived 30 days and had no renal failure (as determined on the basis of urinary output) was assigned a score of 30. If there was renal failure for 10 days and the patient died on day 15, a score of 5 was assigned. To summarize these data, we calculated the total number of failure-free days for all organs as the mean number of days the patients were free of all organ failure.

Statistical Analysis

In this study, we sought to enroll a total of 525 patients who could be evaluated. This figure was based on an expected treatment-related relative reduction in mortality of 35 percent (from 30 percent to 19.5 percent) and a power of 0.80. An independent Data and Safety Monitoring Committee examined the data on each group of 105 patients. Mortality by day 30 was the variable used in considering early termination of the trial (with the O'Brien-Fleming method used to determine sequentially adjusted P values³⁴). After the fourth interim analysis (of 415 patients), the Data and Safety Monitoring Committee was provided with conditional estimates of the power of the study to determine potential differences in mortality between the study groups. A futility index^{35,36} was derived in which mortality by day 30 was treated as a dichotomous outcome variable. Using this information, we stopped the trial after the enrollment of 455 patients.

Short-time-series data were analyzed by deriving the area under the curve of the response variable for each patient, dividing this area by the time the patient spent in the study, and then using a Wilcoxon rank-sum test to compare these univariate statistics.^{37,38} A variety of other approaches were examined, and they yielded similar results.^{39,40} Two-by-two contingency tables were analyzed with a chi-square statistic with Yates' correction for continuity.³⁸ Kaplan-Meier survival curves were compared by the log-rank test.³⁸ Ninety-five percent confidence intervals for proportions were calculated by the method of Fleiss.⁴¹ P values of less than 0.05 were considered to indicate statistical significance.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.*

CHARACTERISTIC	IBUPROFEN (N=224)	PLACEBO (N=231)
Major prognostic indicators		
Age (yr)	54.0±18	56.0±16
APACHE II score	16±7	15±7
Mean blood pressure (mm Hg)	80±17	79±16
Positive culture (% of patients)		
At any site	75	76
Of blood	39	32
Mechanical ventilation (% of patients)	78	76
Adequate antibiotic treatment (% of patients)	96	96
Black race (% of patients)	32	25
Sex (% of patients)		
Female	59	66
Male	42	34
Classification of patient (% of patients)		
Surgical, no trauma	27	25
Surgical, trauma	7	9
Medical	67	66
Laboratory data†		
Serum creatinine (mg/dl)	1.7±1.7	1.5±1.7
Total bilirubin (mg/dl)	1.5±1.7	1.4±1.5
Arterial lactate (mmol/liter)	3.0±3.0	2.7±2.4
PaO ₂ /FiO ₂	214±107	203±102
Pulmonary edema on chest film (% of patients)		
None	11	16
Mild	27	21
Moderate	36	37
Severe	26	26
Organ-system failure at entry (% of patients)‡		
ARDS	29	28
Pulmonary system	56	55
Central nervous system	26	26
Renal system	53	67§
Cardiovascular system	65	63
Organ-system failure (% of patients)		
1 system	6	7
2 systems	36	25
3 systems	35	42
4 systems	21	21
5 systems	2	4
Site of infection (% of patients)		
Lung	46	48
Peritoneum	15	15
Urinary tract	10	10
Other or unknown	30	26

*Plus-minus values are means ±SD. APACHE II denotes Acute Physiology and Chronic Health Evaluation score, PaO₂ partial pressure of arterial oxygen, FiO₂ fraction of inspired oxygen, and ARDS acute respiratory distress syndrome. Because of rounding, percentages do not always total 100.

†To convert values for serum creatinine to micromoles per liter, multiply by 88.4. To convert values for serum bilirubin to micromoles per liter, multiply by 17.1.

‡The various types of organ-system dysfunction are described more fully in the Methods section.

§P=0.002 for the comparison with the ibuprofen group. There were no significant differences between the groups with respect to any other characteristic.

RESULTS

Comparison of Study Groups

The seven centers participating in the trial recruited 455 patients from a total of 3311 patients who fulfilled the study criteria between October 1989 and March 1995. Among the 2862 patients excluded from the study for whom data on 30-day outcomes were available, the mortality rate was 41 percent. The major reasons for exclusion were the need for more than 24 hours to meet the entry criteria and receive the study drug (24 percent of patients), gastrointestinal bleeding (16 percent), inability to obtain consent (12 percent), use of a cyclooxygenase-blocking drug (9 percent), and thrombocytopenia or neutropenia (9 percent). All 455 recruited patients were included in the analyses presented here.

Two hundred twenty-four patients were assigned to the ibuprofen group, and 231 patients were assigned to the placebo group. Table 1 compares the base-line characteristics of the two groups and shows that the groups were balanced with respect to a variety of measures that correlate with mortality and morbidity. The mean (±SD) interval that elapsed from the time the patient met the entry criteria to the administration of the study drug was 10.7±0.6 hours in the ibuprofen group and 11.3±0.6 hours in the placebo group (P not significant). The predominant site of infection was the lung. In each group, infections associated with positive blood cultures were considered to have been treated with appropriate antibiotics in 96 percent of cases (Table 1). Rates of organ dysfunction (organ failure) were similar in the two groups at the time of randomization, except that renal dysfunction was significantly more common in the placebo group.

Ibuprofen, Prostacyclin, and Thromboxane

At enrollment, the patients in both groups excreted substantial amounts of prostacyclin and thromboxane metabolites — approximately 40 and 15 times the normal amounts, respectively. After 44 hours of ibuprofen therapy, the rate of excretion of the prostacyclin metabolite was 11 percent of that in the placebo group and 4 percent of the base-line value; similar reductions were observed in the ibuprofen group with regard to excretion of the thromboxane metabolite (P<0.05). At 20 hours (2 hours after the fourth dose), ibuprofen levels were 24.4±15.0 mg per deciliter.

Physiologic Responses

The use of acetaminophen to reduce temperature was not dealt with in the study protocol. At the time of randomization, 33 percent of the ibuprofen group and 29 percent of the placebo group were receiving acetaminophen for this purpose. As temperatures decreased in the ibuprofen-treated patients, their use of

acetaminophen began to diminish within eight hours. This did not occur in the placebo group. Within the first 24 hours after study-drug administration, the rate of use of acetaminophen decreased to 22 percent in the ibuprofen group, but it increased to 44 percent in the placebo group ($P < 0.001$). The decline in the heart rate during the first eight hours of treatment was significantly greater in the ibuprofen group than in the placebo group ($P < 0.001$). In patients receiving mechanical ventilation, ibuprofen tended to decrease minute ventilation by approximately 2 liters per minute, whereas placebo did not ($P = 0.16$) (Fig. 1). At base line, the mean blood pressure was 80 ± 1 mm Hg in the ibuprofen group and 79 ± 1 mm Hg in the placebo group; at 2 hours, it was 75 ± 1 and 79 ± 1 mm Hg, respectively; and at 24 hours, it was 80 ± 1 and 82 ± 1 mm Hg (P not significant for any of these comparisons).

Mortality and Organ-System Dysfunction

Shock was present at base line in 65 percent of the ibuprofen group and 63 percent of the placebo group. There were no treatment-related differences in the duration of shock. ARDS was present at base line in 29 percent of the ibuprofen group and 28 percent of the placebo group. There was a trend in the ibuprofen group toward more days free of pulmonary dysfunction and ARDS, as well as toward more days free of organ-system failure overall (P not significant) (Fig. 2).

With regard to clinical indications, 59 ibuprofen-treated patients and 51 placebo-treated patients had indwelling pulmonary-artery catheters and measurements of oxygen consumption and delivery at base line and 20 hours after study entry. Among these patients, 56 of those treated with ibuprofen and 46 of those receiving placebo had blood lactate levels available for study. Within 20 hours of study entry, oxygen consumption decreased by 8 percent in the ibuprofen group and increased by 6 percent in the placebo group ($P = 0.046$), and lactate levels decreased by 17 percent and increased by 15 percent, respectively ($P = 0.005$), but oxygen delivery did not change significantly (a decrease of 5 percent as compared with an increase of 2 percent). The lactate levels available in the study population as a whole showed similar reductions with ibuprofen ($P = 0.023$) (Fig. 3).

Mortality by day 30 did not differ significantly in the ibuprofen and placebo groups (37 percent vs. 40 percent) (Table 2). Outcomes in the two groups were also similar when the patients with shock and those with positive blood cultures were studied separately. However, there was a trend toward lower mortality in the ibuprofen group among black patients (42 percent vs. 57 percent, $P = 0.06$) and a significant difference in mortality among patients with hypothermia at entry (54 percent vs. 90 percent, $P = 0.02$).

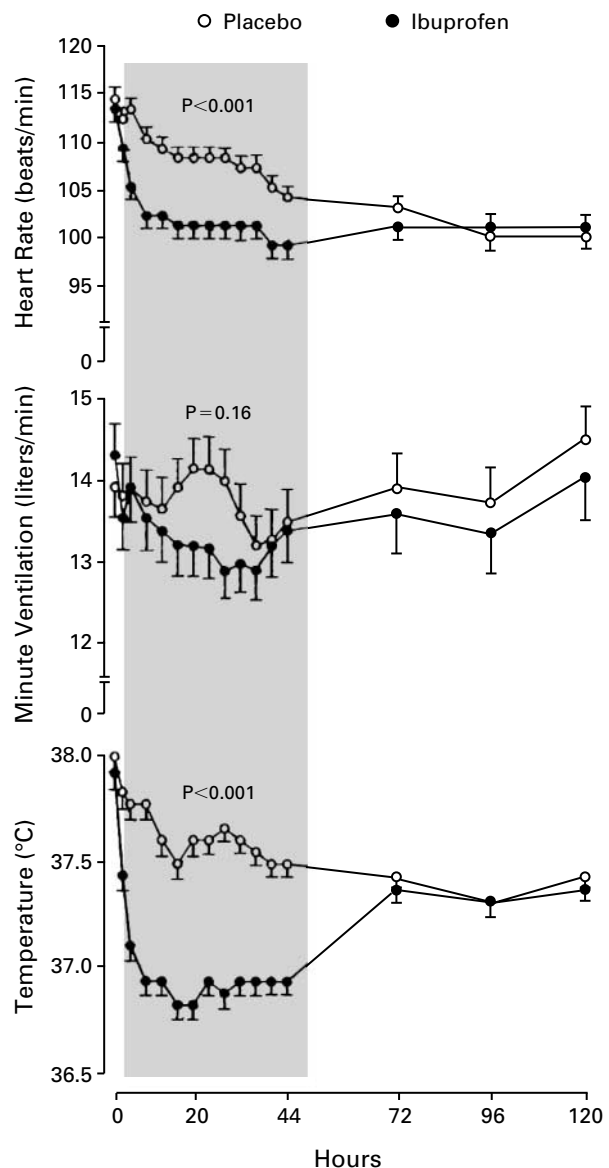


Figure 1. Mean (\pm SE) Temperature, Heart Rate, and Minute Ventilation in the Study Patients.

The shaded area indicates the duration of administration of the study drug. Data on temperature and heart rate are for the entire study population; data on minute ventilation are for intubated patients only (175 patients in the ibuprofen group and 176 patients in the placebo group). P values are for the comparison between the groups with respect to the values measured during the administration of the study drug.

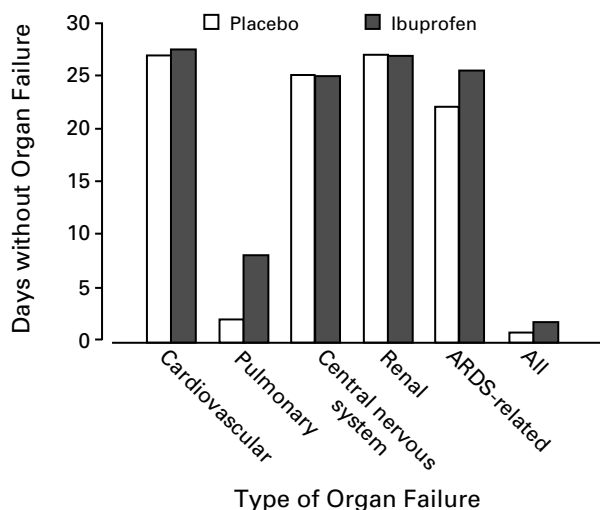


Figure 2. Median Time without Organ Failure during the Study. Bars indicate the median number of days surviving patients were free of each type of organ failure studied and free of all organ failure. Definitions of organ-system dysfunction (organ failure) are given in the Methods section. There were no statistically significant differences between the groups.

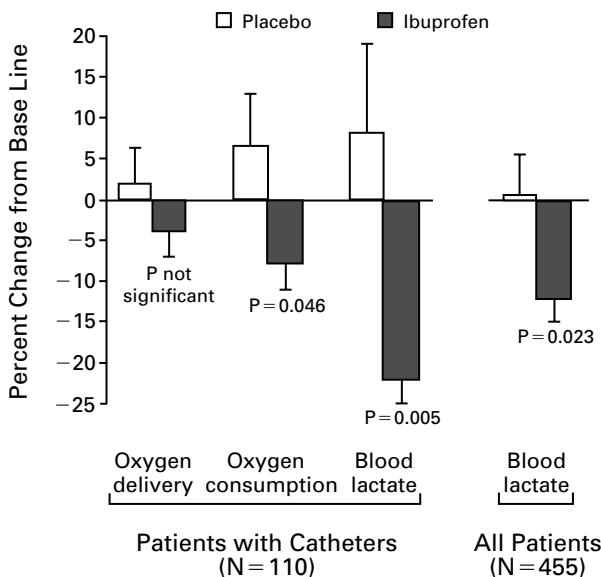


Figure 3. Mean (\pm SE) Percent Changes from Base Line to 20 Hours after Base Line in Oxygen Delivery, Oxygen Consumption, and Blood Lactate Levels among Patients with Pulmonary-Artery Catheters for Whom Data Were Available.

The subgroup of patients with pulmonary-artery catheters included 59 patients in the ibuprofen group and 51 patients in the placebo group.

Complications

Serum creatinine and urinary output were measured serially over a five-day period to evaluate the effects of the study treatment on renal function, and no significant differences were detected between the groups. Hemodialysis was required for the first time in 6 of 224 ibuprofen-treated patients (3 percent) and 13 of 231 placebo-treated patients (6 percent, $P=0.11$). Serial hemoglobin levels did not differ significantly between the two groups, nor were there any marked differences in requirements for transfusion. Gastrointestinal bleeding was reported in 9 patients in the ibuprofen group and 16 patients in the placebo group. During the 30 days of follow-up, distinct second episodes of sepsis occurred in 8.2 percent of the ibuprofen group and 11.1 percent of the placebo group.

DISCUSSION

Ibuprofen was chosen for this trial because studies in both animals and humans in which aspirin,⁴⁻⁶ indomethacin, and ibuprofen were used as inhibitors of cyclooxygenase showed improvement in either the morbidity or the mortality associated with sepsis and because clinical experience with ibuprofen suggested that the drug was safe.^{7-19,22,26-28,42,43} In this study, we demonstrated that ibuprofen reduces fever, tachycardia, and lactic acid levels in patients with sepsis. However, we found no significant effect on mortality or organ failure. Evaluation of renal function and hemorrhagic events failed to demonstrate adverse effects when ibuprofen was administered over a 48-hour period early in the course of sepsis.

In animals in which systemic vasodilatation is prominent, such as primates and dogs with sepsis, ibuprofen increases blood pressure and survival.¹⁷⁻²¹ In a previous clinical study, we found that ibuprofen was associated with a trend toward increased systemic blood pressure, reversal of shock, and normalization of pH.²⁶ In the current trial, we found reductions in lactic acid and oxygen consumption but no changes in oxygen delivery or blood pressure. These changes may be a result of decreased metabolic demand, as evidenced by the lower temperatures and heart rates in the ibuprofen-treated patients, or by improved matching of the delivery of oxygen to its consumption at the tissue level.

The practice of fever control in critically ill patients is controversial. In this study, 44 percent of patients with sepsis received acetaminophen for this purpose, suggesting that many attending physicians desired to limit fever. Even so, temperatures remained significantly elevated in the placebo group, but they returned to normal in the ibuprofen group. These data suggest that acetaminophen was less effective than ibuprofen in reducing temperature in this population of patients.

The analysis of days free of organ failure was per-

TABLE 2. MORTALITY IN PROSPECTIVELY DEFINED SUBGROUPS OF PATIENTS 30 DAYS AFTER ENTRY INTO THE STUDY.*

VARIABLE	IBUPROFEN		PLACEBO	
	NO. OF PATIENTS	MORTALITY (95% CI)	NO. OF PATIENTS	MORTALITY (95% CI)
	%		%	
All patients	224	37 (31–44)	231	40 (34–46)
Shock	146	42 (34–51)	147	45 (37–53)
No shock	78	28 (19–40)	84	31 (22–42)
Black race	72	42 (26–59)	58	57 (37–75)†
Hypothermia	24	54 (20–85)	20	90 (44–99)‡
Positive blood culture	75	45 (34–57)	68	40 (28–52)
Negative blood culture	149	34 (26–42)	163	40 (32–48)

*CI denotes confidence interval.

†P=0.06 for the comparison with the ibuprofen group.

‡P=0.02 for the comparison with the ibuprofen group.

formed to obtain a more sensitive measure of effects than that provided by the analysis of mortality.⁴⁴ This analysis was especially important because of the confounding effect of early mortality on measures such as the duration of organ failure. No consistent effects of ibuprofen treatment were noted with regard to the number of days free of organ failure, the efficiency of oxygenation, findings on chest radiography, or the requirement for mechanical ventilation. This suggests that the effects of ibuprofen on these measures, if any, are fairly small.⁴⁴

High circulating levels of the eicosanoid metabolites of prostacyclin and thromboxane have been associated with increased mortality in patients with sepsis.^{23,24} We found urinary concentrations of prostacyclin metabolites to be approximately 40 times higher than normal, and those of thromboxane metabolites to be approximately 15 times higher than normal. Levels of these metabolites were markedly elevated for at least 48 hours in the placebo group. These findings confirm our earlier work showing marked elevations of eicosanoids in patients with sepsis, with prompt reductions after ibuprofen treatment.

The absence of improved mortality with ibuprofen could have explanations other than the simple lack of efficacy. Perhaps racial differences or physiologic conditions such as hypothermia portend a different response to the drug, as the data in Table 2 show. Selecting the proper dose and duration of ibuprofen treatment is always a concern. Our findings show evidence of marked inhibition of cyclooxygenase, which suggests that the dose of ibuprofen was adequate. However, it is possible that there are effects other than the effects on cyclooxygenase that were not manifested at the dose selected. The treatment period of 48 hours used in this study was based on the information on safety available at the

start of the trial regarding the intravenous formulation of ibuprofen. The data on cyclooxygenase metabolites presented here and in our pilot study indicate that the activity of arachidonic acid metabolites persists for at least several days after the onset of sepsis, as do the corresponding changes in vital signs associated with these mediators. It is thus possible that longer-lasting therapy would have produced different results. Finally, although the patients received the study drug quite early in this study, it is possible that treatment given even earlier, or as prophylaxis, may be necessary to produce effects on mortality and organ failure.^{27,45}

Ibuprofen can have adverse effects, especially on the renal^{21,46} and gastrointestinal⁴⁷ systems. Measuring renal function in terms of days of renal failure, serial creatinine levels, serial determinations of urinary output, and the need for dialysis did not reveal adverse effects, nor did the serial measurement of transfusion requirements, hemoglobin levels, or the incidence of episodes of serious gastrointestinal bleeding show differences between the study groups. The slight decrease in blood pressure (by approximately 4 mm Hg) in the first hours after the administration of ibuprofen was not statistically significant, but it was intriguing nonetheless. Further analysis indicated that this change could be attributed to the influence of patients who entered the trial with hypertension. We speculate that such patients were experiencing pain or other distress, and that ibuprofen, in relieving these underlying causes of hypertension, may have allowed the blood pressure to return toward normal. It did not lower the blood pressure of normotensive or hypotensive patients.

In summary, from this double-blind, randomized, placebo-controlled study of intravenous ibuprofen in patients with sepsis we conclude that treatment with ibuprofen is safe in such patients and markedly reduces the synthesis of prostacyclin and thromboxane, but that it has no effect on survival or the development of shock or ARDS. Treatment with ibuprofen does have clear physiologic effects on fever, tachycardia, oxygen consumption, and lactic acidosis in patients with sepsis.

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APPENDIX

The following additional institutions and investigators participated in the Ibuprofen in Sepsis Study Group: St. Paul's Hospital, Vancouver, B.C., Canada — A. Drummond; the University of Miami School of Medicine and the Department of Veterans Affairs Medical Center, Miami — M. Pena; Louisiana State University Medical Center, New Orleans — B. deBoisblanc,

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REFERENCES

- Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, Wenzel RP. The natural history of the systemic inflammatory response syndrome (SIRS): a prospective study. *JAMA* 1995;273:117-23.
- Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 1992; 101:1644-55.
- Parrillo JE, moderator. Septic shock in humans: advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med* 1990;113:227-42.
- Northover BJ, Subramanian G. Analgesic-antipyretic drugs as antagonists of endotoxin shock in dogs. *J Pathol Bacteriol* 1962;83:463-8.
- Hinshaw LB, Solomon LA, Erdos EG, Reins DA, Gunter BJ. Effects of acetylsalicylic acid on the canine response to endotoxin. *J Pharmacol Exp Ther* 1967;157:665-71.
- Fletcher JR, Ramwell PW. Modification, by aspirin and indomethacin, of the haemodynamic and prostaglandin releasing effects of *E. coli* endotoxin in the dog. *Br J Pharmacol* 1977;61:175-81.
- Parratt JR, Sturgess RM. *E. coli* endotoxin shock in the cat: treatment with indomethacin. *Br J Pharmacol* 1975;53:485-8.
- Idem*. Evidence that prostaglandin release mediates pulmonary vasoconstriction induced by *E. coli* endotoxin. *J Physiol* 1975;246:79P-80P.
- Fletcher JR, Ramwell PW. Indomethacin improves survival after endotoxin in baboons. *Adv Prostaglandin Thromboxane Leukot Res* 1980;7: 821-8.
- Harris RH, Zmudka M, Maddox Y, Ramwell PW, Fletcher JR. Relationships of TxB_2 and 6-keto-PGF $_{1\alpha}$ to the hemodynamic changes during baboon endotoxin shock. *Adv Prostaglandin Thromboxane Leukot Res* 1980;7:843-9.
- Kopolovic R, Thraikill KM, Martin DT, Carey LC, Cloutier CT. A critical comparison of the hematologic, cardiovascular, and pulmonary response to steroids and nonsteroidal anti-inflammatory drugs in a model of sepsis and adult respiratory distress syndrome. *Surgery* 1986;100:679-90.
- Mizus I, Michael J, Sumner W, Gurtner G. Acid aspiration induced pulmonary artery pressure rise is attenuated by hypoxia or ibuprofen. *Crit Care Med* 1983;11:241. abstract.
- Perkowski SZ, Havill AM, Flynn JT, Gee MH. Role of intrapulmonary release of eicosanoids and superoxide anion as mediators of pulmonary dysfunction and endothelial injury in sheep with intermittent complement activation. *Circ Res* 1983;53:574-83.
- Snapper JR, Hutchison AA, Ogletree ML, Brigham KL. Effects of cyclooxygenase inhibitors on the alterations in lung mechanics caused by endotoxemia in the unanesthetized sheep. *J Clin Invest* 1983;72: 63-76.
- Sielaff TD, Sugerman HJ, Tatum JL, Blocher CR. Successful treatment of adult respiratory distress syndrome by histamine and prostaglandin blockade in a porcine *Pseudomonas* model. *Surgery* 1987;102:350-7.
- Wright PE, Bernard GR. Mechanisms of late hemodynamic and airway dynamic responses to endotoxin in awake sheep. *Am Rev Respir Dis* 1989; 140:672-8.
- Almqvist PM, Ekstrom B, Kuenzig M, Haglund U, Schwartz SI. Increased survival of endotoxin-injected dogs treated with methylprednisolone, naloxone, and ibuprofen. *Circ Shock* 1984;14:129-36.
- Fink MP, MacVittie TJ, Casey LC. Inhibition of prostaglandin synthesis restores normal hemodynamics in canine hyperdynamic sepsis. *Ann Surg* 1984;200:619-26.
- Jacobs ER, Soulsby ME, Bone RC, Wilson FJ Jr, Hiller FC. Ibuprofen in canine endotoxin shock. *J Clin Invest* 1982;70:536-41.
- Soulsby ME, Jacobs ER, Perlmutter BH, Bone RC. Protection of myocardial function during endotoxin shock by ibuprofen. *Prostaglandins Leukot Med* 1984;13:295-305.
- Fink MP, MacVittie TJ, Casey LC. Effects of nonsteroidal anti-inflammatory drugs on renal function in septic dogs. *J Surg Res* 1984;36:516-25.
- Hanly PJ, Roberts D, Dobson K, Light RB. Effect of indomethacin on arterial oxygenation in critically ill patients with severe bacterial pneumonia. *Lancet* 1987;1:351-4.
- Halushka PV, Reines HD, Barrow SE, et al. Elevated plasma 6-keto-prostaglandin $\text{F}_{1\alpha}$ in patients in septic shock. *Crit Care Med* 1985;13:451-3.
- Reines HD, Halushka PV, Cook JA, Wise WC, Rambo W. Plasma thromboxane concentrations are raised in patients dying with septic shock. *Lancet* 1982;2:174-5.
- Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988; 318:1481-6.
- Bernard GR, Reines HD, Halushka PV, et al. Prostacyclin and thromboxane A_2 formation is increased in human sepsis syndrome: effects of cyclooxygenase inhibition. *Am Rev Respir Dis* 1991;144:1095-101.
- Galt SW, Bech FR, McDaniel MD, et al. The effect of ibuprofen on cardiac performance during abdominal aortic cross-clamping. *J Vasc Surg* 1991;13:879-83.
- Haupt MT, Jastremski MS, Clemmer TP, Metz CA, Goris GB. Effect of ibuprofen in patients with severe sepsis: a randomized, double-blind, multicenter study. *Crit Care Med* 1991;19:1339-47.
- Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987;317:653-8.
- Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russell JA. Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. *Am J Respir Crit Care Med* 1994;150:318-23.
- Hubbard HL, Eller TD, Mais DE, et al. Extraction of thromboxane B_2 from urine using an immobilized antibody column for subsequent analysis by gas chromatography-mass spectrometry. *Prostaglandins* 1987;33: 149-60.
- Christman BW, Christman JW, Dworski R, Blair IA, Prakash C. Prostaglandin E_2 limits arachidonic acid availability and inhibits leukotriene B_4 synthesis in rat alveolar macrophages by a nonphospholipase A_2 mechanism. *J Immunol* 1993;151:2096-104.
- Lockwood GF, Wagner JG. High-performance liquid chromatographic determination of ibuprofen and its major metabolites in biological fluids. *J Chromatogr* 1982;232:335-43.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979;35:549-56.
- Ware JH, Muller JE, Braunwald E. The futility index: an approach to the cost-effective termination of randomized clinical trials. *Am J Med* 1985;78:635-43.
- Halperin M, Lan KKG, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. *Control Clin Trials* 1982;3: 311-23.
- Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;300:230-5.
- Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford, England: Blackwell Scientific, 1994.
- SAS/STAT software: changes and enhancements, release 6.07. Technical report P-229. Cary, N.C.: SAS Institute, 1992.
- Latour D, Latour K, Wolfinger RD. Getting started with PROC MIXED. Cary, N.C.: SAS Institute, 1994.
- Fleiss JL. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley, 1981:13-4.
- Rinaldo JE, Dauber JH. Effect of methylprednisolone and of ibuprofen, a nonsteroidal antiinflammatory agent, on bronchoalveolar inflammation following endotoxemia. *Circ Shock* 1985;16:195-203.
- Rinaldo JE, Pennock B. Effects of ibuprofen on endotoxin-induced alveolitis: biphasic dose response and dissociation between inflammation and hypoxemia. *Am J Med Sci* 1986;291:29-38.
- Bernard GR, Doig G, Hudson LD, et al. Quantification of organ failure for clinical trials and clinical practice. *Am J Respir Crit Care Med* 1995; 151:Suppl:A323. abstract.
- Huval WV, Lelcuk S, Allen PD, Mannick JA, Shepro D, Hechtman HB. Determinants of cardiovascular stability during abdominal aortic aneurysmectomy (AAA). *Ann Surg* 1984;199:216-22.
- Delmas PD. Non-steroidal anti-inflammatory drugs and renal function. *Br J Rheumatol* 1995;34:Suppl 1:25-8.
- Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994;330:377-81.

CORRECTION

Ibuprofen in Patients with Sepsis

To the Editor: Bernard et al. (March 27 issue)¹ report the results of a double-blind, randomized, placebo-controlled study of intravenous ibuprofen in patients with sepsis. They conclude that treatment with ibuprofen is safe in these patients and has a favorable effect on fever, tachycardia, oxygen consumption, and lactic acidosis, but not on mortality. We are concerned about this report and its conclusions.

There is abundant evidence that arachidonic acid metabolites act as endogenous regulators of cytokine production.² Prostaglandin E₂ inhibits the release of interleukin-1 and tumor necrosis factor α (TNF- α).³ We tested the effect of ibuprofen on serum levels of TNF- α and interleukin-6 in humans.⁴ After the injection of lipopolysaccharide, the respective serum levels of interleukin-6, TNF- α , and elastase were 4.2, 1.7, and 1.5 times as high in subjects who received two doses of ibuprofen (800 mg each) as in controls.⁴ In addition, high TNF- α concentrations primed neutrophils for degranulation in vitro.⁴ Since the mortality rate associated with sepsis correlates with high interleukin-6 and TNF- α levels, the use of prostaglandin inhibitors in sepsis may be harmful.

As a rationale for the study, Bernard et al.¹ cite only the animal models and clinical studies in which the effects of nonsteroidal antiinflammatory drugs were favorable. However, in five controlled trials of antipyretic agents in nonhuman mammals with severe infection, mortality was increased in animals given prostaglandin inhibitors (relative risk, 2.04; 95 percent confidence interval, 1.19 to 4.51).⁵ In the study by Bernard et al.,¹ ibuprofen did not have serious side effects. However, prostaglandin inhibitors raise cytokine levels during endotoxemia, and high levels of cytokines correlate with mortality. Therefore, prostaglandin inhibitors should be used with caution in patients with sepsis.

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References

- Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. *N Engl J Med* 1997;336:912-918.
- Chouaib S, Bertoglio JH. Prostaglandins E as modulators of the immune response. *Lymphokine Res* 1988;7:237-245.
- Knudsen PJ, Dinarello CA, Strom TB. Prostaglandins posttranscriptionally inhibit monocyte expression of interleukin 1 activity by increasing intracellular cyclic adenosine monophosphate. *J Immunol* 1986;137:3189-3194.
- Spinas GA, Bloesch D, Keller U, Zimmerli W, Cammisuli S. Pre-treatment with ibuprofen augments circulating tumor necrosis factor- α , interleukin-6, and elastase during acute endotoxemia. *J Infect Dis* 1991;163:89-95.
- Shann F. Antipyretics in severe sepsis. *Lancet* 1995;345:338-338.

The authors reply:

To the Editor: Drs. Zimmerli and Widmer fear that treatment of fever with nonsteroidal antiinflammatory drugs (NSAIDs) may be harmful in the light of data on five animal models.¹ Without discussing the virtues and limitations of each of these models, we acknowledge that there is potential harm from such treatment. On the other hand, as we stated in our paper, many more reports show significant benefit, including improved survival. When we began our trial, the substantial data on ibuprofen in animals, on balance, favored a beneficial effect of ibuprofen.

Concern that ibuprofen may augment TNF (and other biologically active compounds) is well taken. However, even if NSAIDs raise TNF levels in patients with sepsis, it is not clear that physiology or survival is adversely affected. Perhaps TNF levels are physiologically irrelevant in the presence of cyclooxygenase blockade. In the endotoxin experiments conducted by Zimmerli and Widmer as well as by others,² all clinical effects of endotoxin administration, including headaches, nausea, chills, fever, and myalgia, were ameliorated by concomitant administration of ibuprofen. The subjects could not tell whether they had received endotoxin or placebo.

Arguments for and against the relative benefit of TNF antagonism in sepsis from an immunomodulatory perspective are ongoing and were discussed in the editorial accompanying our article.³ Zimmerli and Widmer and others² present data that suggest that ibuprofen may increase circulating TNF levels in sepsis. However, it remains open to question whether this is harmful or beneficial, since in at least one trial TNF antagonism appeared to worsen the outcome in patients with sepsis.⁴ Though we know of no additional studies of ibuprofen that are planned or under way, several trials involving various methods of TNF inhibition are under way that may answer some of these questions. Preclinical experiments cannot answer the risk-benefit question with respect to humans with sepsis; they can only suggest where potential problems and efficacy may lie. Hence, clinical trials such as ours are designed to determine the net result of the inhibition of each component of the human response to severe sepsis, be it TNF, prostaglandins, or something else.

Table 2 of our report included incorrect confidence intervals for the black race and hypothermia subgroups. The mortality rate was 42 percent (95 percent confidence interval, 30 to 54 percent) among ibuprofen-treated black patients and 57 percent (95 percent confidence interval, 43 to 70 percent) among black patients given placebo (P = 0.12). The mortality rate was 54 percent (95 percent confidence interval, 33 to 74 percent) among ibuprofen-treated patients with hy-

pothemia and 90 percent (95 percent confidence interval, 67 to 98 percent) among placebo-treated patients with hypothermia ($P = 0.02$).

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References

1. Shann F. Antipyretics in severe sepsis. *Lancet* 1995;345:338-338.
2. Michie HR, Manogue KR, Spriggs DR, et al. Detection of circulating tumor necrosis factor after endotoxin administration. *N Engl J Med* 1988;318:1481-1486.
3. Warren HS. Strategies for the treatment of sepsis. *N Engl J Med* 1997;336:952-953.
4. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor:Fc fusion protein. *N Engl J Med* 1996;334:1697-1702.