Effect of Pentoxifylline in Severe Sepsis

Results of a Randomized, Double-blind, Placebo-Controlled Study

Karl-Hermann Staubach, MD; Jörg Schröder, MD; Frank Stüber, MD; Katrin Gehrke, MD; Emanuel Traumann, MD; Peter Zabel, MD

Objective: To evaluate the effect of pentoxifylline on organ dysfunction, survival, and mediator response in patients with severe sepsis.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Surgical intensive care units at 2 university hospitals.

Patients: Fifty-one surgical patients with severe sepsis were randomized to receive pentoxifylline continuously (27 patients) or saline infusion as placebo (24 patients).

Interventions: Patients received pentoxifylline (1 mg/kg of body weight per hour; maximum, 1800 mg/d) during 28 days or until they were discharged from the intensive care unit or died.

Measurements and Main Results: Vital signs and organ function were determined at diagnosis; daily from day 1 to 7; on days 10, 14, 17, 21, and 24; and 28 days after diagnosis of sepsis. There were no differences in characteristics of patients at diagnosis in the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (mean±SEM, 17±4 points for the pentoxifylline group and 18±5 points for the placebo group), the multiple organ dysfunction score (mean±SEM, 11.0±0.8 vs 11.8±1.0 points), tumor necrosis factor α and interleukin 6 bioactivity, serum endotoxin levels, or organ dysfunction. At study entrance, 23 of 27 patients in the pentoxifylline group and 21 of 24 patients in the placebo group experienced septic shock. No adverse effects of pentoxifylline treatment were observed. The 28-day mortality rate was 30% (8/27) in pentoxifylline-treated patients and 33% (8/24) in the placebo group. Hospital mortality was 41% (11/27) in the pentoxifylline group and 54% (13/24) in the placebo group. The multiple organ dysfunction score decreased in patients receiving pentoxifylline 4 days after diagnosis of sepsis compared with placebo-treated patients; a significant difference was reached on day 14 (P<.05; Student t test, Bonferroni correction). The PaO2/FIO2 (fraction of inspired oxygen) ratio was significantly improved in pentoxifylline-treated patients on days 14 and 17 (P<.05), and the pressure-adjusted heart rate was significantly improved on day 6 (P<.05) compared with the placebo group. Serum endotoxin levels, tumor necrosis factor α and interleukin 6 bioactivity were not different between the groups during the study.

Conclusions: Continuous intravenous administration of pentoxifylline beneficially influenced cardiopulmonary dysfunction in patients with sepsis without adverse effects. Larger trials are needed to evaluate the efficacy in improving organ function in relation to the outcome for patients with severe sepsis.

Arch Surg. 1998;133:94-100

Sepsis carries an exceedingly high mortality rate that has not decreased during the last decade despite advances in molecular biology and immunology. In the complex endogenous mediator cascade of sepsis and subsequent multiple organ dysfunction, proinflammatory cytokines have a key role. Tumor necrosis factor α (TNF-α) is regarded as a central mediator, and many attempts have been made to block TNF-α. However, in clinical trials, none of these TNF-α–blocking substances revealed clinical benefit in survival.

Tumor necrosis factor α–blocking strategies with monoclonal antibodies were related to short-term therapy in the initial phase of sepsis because of the immunogenic potential of these substances. Total blockade of this central mediator has led to increased mortality in human studies because TNF-α to some extent is essential for the endogenous defense response to infection.

Compounds such as pentoxifylline, with properties to reduce TNF-α production, seem to induce a balanced synthesis of TNF-α and may overcome
PATIENTS AND METHODS

STUDY DESIGN

The study was performed in the surgical intensive care units (ICUs) of 2 centers (University of Kiel, Kiel, and University of Lübeck, Lübeck, Germany) as a randomized, double-blind, and placebo-controlled study of patients with severe sepsis. The protocol was approved by the ethics committees of the Christian-Albrechts University of Kiel and the Medical School, University of Lübeck. Written informed consent was obtained from all patients or their relatives. Patients received full intensive care treatment for sepsis including fluid resuscitation, vasopressors, ventilatory support, hemofiltration, antibiotics, and surgical procedures as required. All treatment of the patients was provided by physicians who were not involved in the study.

PATIENT SELECTION

Patients eligible for this study were those with severe sepsis or septic shock according to the definition of Bone et al.21 Septic shock was defined as a sustained decrease in systolic blood pressure to less than 90 mm Hg or a decrease of 40 mm Hg from baseline in the absence of an hypertensive agents, despite adequate fluid resuscitation.

Patients were excluded for any of the following reasons: younger than 18 years; suspected pregnancy; uncontrollable hemorrhage; cardiogenic shock; burns; severe, pre-existing, parenchymal hepatic disease with clinically significant portal hypertension; previous therapy with glucocorticoids, methylxanthine derivatives, amnnone, or non-steroidal anti-inflammatory drugs; previous irradiation or chemotherapy; or participation in ongoing or previous clinical trials using anti-inflammatory agents. Organ transplant recipients and patients with hematologic malignant neoplasms as an acute underlying condition were not enrolled. Fifty-one surgical patients were randomly assigned to a maximum of 1800 mg/d or normal saline solution as placebo during 28 days or until patients were discharged from the ICU or died.

CLINICAL EVALUATION

All patients were followed up throughout their hospital stay. Vital signs were monitored at diagnosis of sepsis and during the 28-day study or until patients were discharged from the ICU or died.

Daily at 8 AM from day 1 to 7; on days 10, 14, 17, 21, and 24; and on day 28, blood samples for pentoxifylline determination and for hematologic or biochemical measurements were obtained. The following data were recorded: serum endotoxin levels, proinflammatory cytokine levels (TNF-α, interleukin 6 [IL-6]), and values for the calculation of the multiple organ dysfunction score according to Marshall et al22; values for the calculation of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score23; and values for organ dysfunction. Pulmonary dysfunction was characterized by the worst PaO2/FiO2 (fraction of inspired oxygen) ratio; cardiovascular dysfunction was monitored by the pressure-adjusted heart rate (central venous pressure times the heart rate divided by the mean arterial pressure). Hepatic dysfunction was described by total bilirubin, and renal dysfunction was characterized by the creatinine serum concentration. The serum lactate concentration was determined, and systemic hemodynamics were monitored using pulmonary artery catheters (Thermodilution Catheter, Arrow, Reading, Pa) at diagnosis of severe sepsis. The primary source of sepsis was documented by the investigators at enrollment. Causative organisms were identified from blood or body fluid, and adequate antimicrobial therapy was determined by an infectious disease specialist not involved in the study.

MEASUREMENTS

Blood samples were centrifuged at 1000 g for 10 minutes, and serum for the cytokine determination was collected in sterile tubes. Samples for endotoxin determination were collected in Endotube ET (Chromogenix AB, Mölndal, Sweden). Endotoxin and serum samples were coded with numbers and stored at −70°C until assayed at the Research Institute of Borstel, Borstel, Germany, without knowing the treatment group. Serum concentrations of endotoxin were measured using the limulus lysate test24 with a detection limit of 0.012 Ehrlich U/mL. The biological activity of TNF-α was determined by its cytotoxic effect on the fibrosarcoma cell line, WEHI 164 subclone 13.25 The detection limit of the assay was 2 pg/mL. The IL-6 bioactivity was measured using the specific IL-6-dependent murine hybridoma cell line, B 13-29 subclone 9,26 with a detection limit of 1.25 pg/mL. All cytokine samples were analyzed in duplicate. Pentoxifylline concentrations were measured by gas-liquid chromatography described by Bryce and Burrows27 with a detection limit of 3 ng/mL.

STATISTICAL ANALYSIS

Data are expressed as the mean±SEM. The statistical analysis for normally distributed data was performed with unpaired Student t test with Bonferroni correction for multiple comparisons to test differences between the groups. Nonparametric comparisons were evaluated with the Mann-Whitney U test. The χ2 test was used to compare patient characteristics between groups at enrollment in the study. The 28-day and in-hospital survival rates were estimated in each of the treatment groups using the Kaplan-Meier method, and these estimates were compared with the log-rank test. Differences were considered significant at P<.05.

these problems, offering the potential of long-term therapy.7 Pentoxifylline is a methylxanthine derivative that has been used for treatment of chronic occlusive arterial disease because of its rheological actions.8 Pentoxifylline is known to inhibit phosphodiesterase, thereby increasing cytoplasmic cyclic adenosine monophosphate levels, and elevation of cyclic adenosine monophosphate strongly inhibits TNF-α gene transcription.9 In animal experiments and in humans challenged with endotoxin, down-regulation of TNF-α could be induced by the application of pentoxifylline.10,11 In addition to its beneficial effects on microcirculation,12 pen-
toxifylline has inhibitory effects on cytokine-induced neutrophil activation and expression of adhesion molecules.\textsuperscript{13} Based on beneficial effects in experimental endotoxic shock, lung injury, and sepsis, clinical trials with pentoxifylline remained warranted.\textsuperscript{14-17} Short-term pilot studies of large doses of pentoxifylline in humans failed to demonstrate any adverse pulmonary or hemodynamic effects.\textsuperscript{18-20}

The purpose of this study, therefore, was to evaluate the effect on multiple organ dysfunction, outcome, and mediator response of high-dose and long-term administration of pentoxifylline as adjunctive therapy in severe sepsis.

**RESULTS**

There were no differences in patients assigned to receive pentoxifylline or placebo treatment in age, sex, or underlying disease (Table 1). Almost 90% of patients in both groups experienced septic shock (Table 2). Eighteen patients in the pentoxifylline group had peritonitis compared with 12 patients in the placebo group. Eight patients in the placebo group and 4 in the pentoxifylline group had necrotizing pancreatitis ($P=.14$). Other causes of sepsis included severe soft tissue infection (2 patients), postoperative sepsis (4 patients), mediastinitis (2 patients), and adult respiratory distress syndrome (1 patient).

There was no difference in the APACHE II score, the multiple organ dysfunction score, single organ dysfunction, or endotoxin or cytokine levels at diagnosis of sepsis, indicating that patients were well matched for severity of sepsis (Table 2). The 28-day mortality rate was 30% (8/27) in patients receiving pentoxifylline and 33% (8/24) in the placebo group. In-hospital mortality was 41% (11/27) in the pentoxifylline group and 54% (13/24) in the placebo group (Figure 1). There were no significant differences in the survival curves of the groups (log-rank analysis, $P=.85$ for 28-day survival and $P=.43$ for hospital survival). Adverse effects were not reported in any patient.

For the combined treatment groups, the causative microorganism was gram-negative in 11 (22%) of the patients, gram-positive in 12 (24%), and mixed gram-negative and gram-positive in 19 (37%). Six patients had a combination of bacteria and fungi, and 3 patients had no documented bacteria or fungi. The microorganisms causing infections were equally distributed in the treatment groups.

At baseline, the multiple organ dysfunction score was not different between the groups. From day 4 after the diagnosis of sepsis, the score decreased in patients receiving pentoxifylline compared with placebo-infused patients (Figure 2). This difference reached significance on day 14 after the diagnosis of sepsis ($P<.05$). The $\text{PaO}_2/\text{FiO}_2$ ratio as a parameter for pulmonary dysfunction increased from day 7 in patients receiving pentoxifylline compared with patients receiving placebo (Figure 3). The difference was statistically significant on days 14 and 17 after the diagnosis of severe sepsis ($P<.05$).

---

### Table 1. Demographic Data of Patients With Severe Sepsis Assigned to Receive Pentoxifylline or Placebo

<table>
<thead>
<tr>
<th></th>
<th>Pentoxifylline Group</th>
<th>Placebo Group</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SEM)</td>
<td>54.0±3.3</td>
<td>58.0±2.7</td>
<td>.37</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>6/21</td>
<td>6/18</td>
<td>.82</td>
</tr>
<tr>
<td>Underlying disease*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5</td>
<td>6</td>
<td>.57</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>1</td>
<td>.20</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2</td>
<td>2</td>
<td>.90</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>6</td>
<td>9</td>
<td>.23</td>
</tr>
<tr>
<td>Nonhematologic cancer</td>
<td>6</td>
<td>8</td>
<td>.38</td>
</tr>
</tbody>
</table>

* Some patients had more than 1 underlying disease.

### Table 2. Severity of Sepsis at Enrollment*

<table>
<thead>
<tr>
<th></th>
<th>Pentoxifylline Group</th>
<th>Placebo Group</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II score</td>
<td>17.1±0.9</td>
<td>18.8±1.0</td>
<td>.21</td>
</tr>
<tr>
<td>MOD score</td>
<td>11.0±0.6</td>
<td>11.8±1.0</td>
<td>.50</td>
</tr>
<tr>
<td>Septic shock (No. of patients with shock/total No. of patients)</td>
<td>23/27</td>
<td>21/24</td>
<td>.81</td>
</tr>
</tbody>
</table>

* The values are mean±SEM and median (interquartile range) for endotoxin or cytokine determination. APACHE indicates Acute Physiology and Chronic Health Evaluation; MOD, multiple organ dysfunction; $\text{FiO}_2$, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PAHR, pressure-adjusted heart rate; CI, cardiac index; SVR, systemic vascular resistance; LPS, lipopolysaccharide or endotoxin; TNF-$\alpha$, tumor necrosis factor $\alpha$; and IL-6, interleukin 6.

©1998 American Medical Association. All rights reserved.
The pressure-adjusted heart rate characterizing cardiac function was significantly different on day 6 after diagnosis (P < .05) and remained decreased compared with the placebo group (Figure 4). The total bilirubin as a measure of hepatic dysfunction, serum creatinine as a measure of renal dysfunction, and the platelet count as a measure of hematologic dysfunction showed no differences throughout the evaluation. The serum endotoxin concentrations and IL-6 and TNF-α bioactivity were not significantly different in the groups during the study. The median serum concentration of pentoxifylline was 3628 ng/mL on the first day after starting infusion and 1620 ng/mL on day 2; it reached a steady state from day 3 until the end of the 28-day study. A similar pattern was demonstrated for the first metabolite of pentoxifylline (BL 194) with a 1.3- to 2.5-fold higher serum concentration than the parent drug (Figure 5).
In this randomized, double-blind, placebo-controlled clinical trial, different scores, measures of organ dysfunction, and biological markers (ie, endotoxin, TNF-α, and IL-6) defined a patient population with severe sepsis. Patient groups assigned to receive pentoxifylline or placebo in addition to standard therapy for sepsis were well matched in severity of disease. In this study, only surgical patients with severe sepsis were included to make the patient population more homogeneous, because previous multicenter clinical studies that failed to demonstrate a beneficial effect were characterized by a heterogeneous patient population.28

Organ dysfunction values were used as valid end points,29 and mortality was not restricted to the conventional 28-day survival. In-hospital survival was considered as an additional variable demonstrating an increased mortality compared with the 28-day rate. One third of all nonsurvivors died after the end of the study; there was a 13% lower mortality rate in the pentoxifylline-treated group, which was not a significant difference in this small trial. In-hospital mortality may become an additional variable in further sepsis trials, but a clear cut-off point must be determined to define it.

There has been a lack of formal consensus on the criteria used to define the degree of organ dysfunction.30 Based on the studies of Marshall et al,22 the optimal descriptors for multiple organ dysfunction were used in this study to characterize the degree of single organ dysfunction, while the multiple organ dysfunction syndrome as the clinical end point was described by the multiple organ dysfunction score.

A systemic microcirculatory injury is considered a fundamental problem in the development of organ dysfunction and sepsis. The excessive production of various mediators released by neutrophils and macrophages induces an increased endothelial permeability with organ edema and depressed organ function,2 which is known to be genetically determined and associated with a poor prognosis.31 Meanwhile, clinical data confirm experimental evidence that TNF-α must be considered as the central mediator of sepsis,2 which might be common for gram-negative and gram-positive infections.32 In this study, gram-positive bacteria or a combination of gram-positive and gram-negative bacteria exceeded gram-negative bacteria as cause of sepsis, indicating that anti-TNF-α strategies may become the most promising treatment modality in sepsis.

Pentoxifylline has a clear inhibitory effect on TNF-α production by the macrophages and on circulatory levels in animal studies,9 but the pentoxifylline dose used in most of the animal studies was up to 10-fold higher compared with the amount used in clinical studies. In a guinea pig lung injury model, however, it was demonstrated that a dose of 3 mg/kg of body weight was as effective as higher doses.31 In humans, continuous intravenous application with doses up to 1.5 mg/kg have been used.18,20 Despite the half-life of 30 minutes, continuous venous application with doses up to 1.5 mg/kg of body weight per hour) associated with a 2-fold increased plasma concentration of pentoxifylline after 24 hours. However, the clinical significance of the detection of TNF-α in critically ill patients varies in different series because of the short half-life of TNF-α,34 the timing of measurement, the method used, or the influence of circulating TNF-α inhibitors.35 Tumor necrosis factor α is usually produced locally within organs and tissues, acting more as a paracrine or autocrine mediator. Therefore, serum levels of TNF-α may not reflect TNF-α bioactivity.36 Our study again highlighted the difficulties of designing anti-TNF-α strategies based on circulating TNF-α levels because it was difficult to correlate serum or plasma levels of a particular proinflammatory cytokine with the overall extent of tissue damage.37

Interventions that interfere with several arms of the mediator cascade may become adjuvant treatment modalities in the future, because in sepsis and septic shock, the release of various mediators has progressed already considerably. Pentoxifylline, a methylxanthine derivative with TNF-α–inhibiting properties, has been highly protective in different animal models of endotoxin shock, sepsis, and ischemia and reperfusion. This study provides further evidence that pentoxifylline must be considered as a clinically relevant therapy for the treatment of sepsis-induced multiple organ dysfunction in humans. The results of this study, with significant improvement of cardiopulmonary dysfunction, demonstrate that continuous high-dose administration of pentoxifylline as long-term therapy is effective without producing adverse effects. However, this study again highlighted the difficulties to base studies with anti–proinflammatory strategies on circulating mediator levels. Concentrations of TNF-α or other cytokines are influenced by numerous factors and may represent only serum activity but not organ or tissue activity. In a homogeneous surgical population, a significant reduction in the multiple organ dysfunction score during the second and third weeks after diagnosis of sepsis was demonstrated, resulting in an improved in-hospital survival rate. This trend, however, was not significant in this small trial, but further studies with enrollment of a higher number of patients are needed to evaluate improvement of survival.
similar to those observed for pentoxifylline.38 Usually, levels of the first metabolite are 3- to 5-fold greater than the parent drug, while in this study, the levels of BL 194 were 1.3- to 2.5-fold higher than the pentoxifylline serum concentration. In patients with severe sepsis, oxygenation or cardiac function may be affected by mechanical ventilation or variability in the use of inotropic agents. However, no differences in mechanical ventilation, the number of patients who received inotropic drugs, or the concentration of inotropic agents given could be found (data not shown). This indicates that the improvement of cardiopulmonary function was effected by pentoxifylline, resulting in a decreased multiple organ dysfunction score. The mechanism to improve pulmonary function may be the down-regulatory effect of pentoxifylline on neutrophils with attenuation of alveolar microvascular leakage.40 In addition, pentoxifylline may directly or indirectly increase myocardial contractility, resulting in improved cardiac function.41

Continuous intravenous administration of pentoxifylline beneficially influenced organ function without adverse effects. Pentoxifylline, an inexpensive, readily available agent, has the potential of long-term administration and holds promise as an agent for the treatment of severe sepsis. The clinical efficacy of pentoxifylline in relation to organ dysfunction, survival, and mediator response, however, must be evaluated in further studies, especially with regard to dose dependency.

Presented at the 17th Annual Meeting of the Surgical Infection Society, Pittsburgh, Pa, May 1, 1997.

The study was supported in part by Dr Rentschler Arzneimittel GmbH, Laepheim, Germany.

Corresponding author: Jörg Schröder MD, Department of General and Thoracic Surgery, University of Kiel, Arnold-Heller-Strasse 7, 24105 Kiel, Germany.

REFERENCES

3. Christman JW, Holden EP, Blackwell TS. Strategies for blocking the systemic response, however, must be evaluated in further studies, especially with regard to dose dependency.

The study was supported in part by Dr Rentschler Arzneimittel GmbH, Laepheim, Germany.

Corresponding author: Jörg Schröder, MD, Department of General and Thoracic Surgery, University of Kiel, Arnold-Heller-Strasse 7, 24105 Kiel, Germany.

REFERENCES

3. Christman JW, Holden EP, Blackwell TS. Strategies for blocking the systemic response, however, must be evaluated in further studies, especially with regard to dose dependency.

The study was supported in part by Dr Rentschler Arzneimittel GmbH, Laepheim, Germany.

Corresponding author: Jörg Schröder, MD, Department of General and Thoracic Surgery, University of Kiel, Arnold-Heller-Strasse 7, 24105 Kiel, Germany.

REFERENCES


Stephen F. Lowry, MD, New York, NY: Let me ask a couple of specific questions related to the conduct of the study. One is about dose dependency and dose adequacy. When one reads through your article, there is some question as to whether you have achieved the desired pharmacologic activity. The new data that you presented regarding mean arterial pressure alludes mechanistically to indeed a phosphodiesterase effect. Do you have any other confirmatory data to suggest that you are achieving this activity at the cellular level, for example, in an ex vivo modeling system?

What about length of stay in the ICU and survival time issues that have been of recent interest to investigators and regulators?

Finaly, you have been very optimistic about moving forward with this as a larger phase 2 or even a phase 3 trial. I am not sure I share that enthusiasm because of the rather modest differences in primary 28-day mortality. How many patients would be required to really observe a meaningful difference if you undertook such a study?

John C. Marshall, MD, Toronto, Ontario: Obviously, this is a complex group of patients with a number of differing co-interventions and a variety of influences that impact on mortality, and you would not expect to see a mortality impact in such a small population. But I was very intrigued by what you did show, namely, a physiologic effect that was primarily cardiorespiratory in nature. Did those physiologic benefits reflected in changes in cardiovascular and respiratory dysfunction have a beneficial impact on renal dysfunction, hepatic dysfunction, or other organ system dysfunction, or are you seeing a pharmacologic effect that is exclusively cardiorespiratory in nature?

Timothy G. Buchman, PhD, St Louis, Mo: Following up on Dr Marshall’s question, I wonder whether the effects that you are seeing might not be mediated through a pathway different than the inflammatory mediators? Pentoxifylline has been suggested at various times to stabilize the calcium dyshomeostasis, which we see in this process. Do you have data on the stability of the calcium in these patients, and is it possible that the preferential effects on the cardiopulmonary system may be reflected through a stabilization of calcium levels?

Philip S. Barie, MD, New York: I wonder if you could comment on the temporal relationships between the timing of intervention and the fact that the physiologic responses you observed became meaningful statistically at 7 to as many as 14 days thereafter? When we resuscitate patients clinically in septic shock, we are looking for hemodynamic improvement within hours, or certainly within a day or two. The longer you go from an intervention to a response in an ICU setting, where it is almost impossible to control for all of the clinical variables, you get a bias where as time goes by, the consequence becomes increasingly difficult to relate to the cause. When we look at our patients longitudinally in terms of outcome from organ dysfunction, we see survivors discriminating from nonsurvivors much earlier than you have identified these physiologic changes.

Dr Schröder: Dr Lowry, with respect to your first question concerning the dose dependency, the optimal dose of pentoxifylline is still an open issue, as I already mentioned. Zeni and coworkers published a study using a higher dose with 1.5 mg/kg of body weight over 48 hours and found a 2-fold increase in serum concentration of pentoxifylline and the first metabolite using a comparable method. This may indicate that higher doses are more beneficial than the dose we used (1 mg/kg of body weight). Concerning the question of differences in mean arterial pressure, we found no difference between the treatment groups in terms of use of vasopressors or volume resuscitation. Attenuation of the drop of mean pressure up to day 5 after diagnosis of sepsis, therefore, seems to be related to pentoxifylline administration. With regard to Dr Barie’s question, we only used 2 surgical centers to make the patient population more homogeneous and to be able to compare patients with similar therapeutic modalities, which on the other hand resulted in a trial with a relatively small number of patients.

The beneficial effects on organ dysfunction especially on cardiopulmonary parameters had no significant impact on 28-day or hospital mortality rate, as I already demonstrated. With respect to ICU stay or hospital stay, no significant difference with a median ICU stay of 26 days for patients receiving pentoxifylline and 21 days for patients receiving placebo, and 41 vs 40 days for hospital stay could be demonstrated. The patient number is too small to draw any definitive conclusion, and we are looking forward to a larger trial to confirm these beneficial effects, especially with regard to survival, ICU stay, or hospital stay. However, for a multicenter trial, we will need a few hundred patients with center differences and inhomogeneity of patient population. Therefore, we preferred and would like to continue to include only surgical patients with sepsis in northern Germany to minimize center differences and patient inhomogeneity.

With regard to glucocorticoids, we excluded those patients who received any kind of immunosuppression, and none of the study patients received glucocorticoids during the evaluation. Patients were included within 12 hours, which was possible because the authors were on call to include those patients with the clinical diagnosis of sepsis. This study again highlights the problem to base such kind of study on systemic determination of TNF. The question was raised, if there is a local effect of pentoxifylline. Despite the fact that we could not demonstrate a systemic effect, I would suggest that there is a beneficial local effect. In animal studies, pentoxifylline inhibited granulocyte neutrophil functions, attenuated pulmonary microvascular edema, and could reduce the negative inotropic effect of TNF. The beneficial effect of TNF on cardiopulmonary dysfunction may be indirect evidence for local TNF inhibition resulting in improved $\text{P}_\text{a}O_2$/FiO$_2$ ratio, increased mean arterial pressure and lower pressure-adjusted heart rate compared with placebo-treated patients. No data were obtained with regard to the effect of pentoxifylline on calcium metabolism or on other issues like prostaglandin values. The effects on cardiopulmonary dysfunction were described in the early phase of sepsis, but we have no explanation why a significant effect on pulmonary dysfunction could be presented only in the second week of the septic course. This may be answered in further studies.