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Sivelestat, a Neutrophil Elastase Inhibitor, Reduces Mortality Rate of Critically Ill Patients

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HOSHI, K., KUROSAWA, S., KATOH, M., ANDOH, K., SATOH, D. and KAISE, A. *Sivelestat, a Neutrophil Elastase Inhibitor, Reduces Mortality Rate of Critically Ill Patients*. Tohoku J. Exp. Med., 2005, **207** (2) 143-148 —— Many studies have suggested that neutrophil elastase (NE) may contribute to multiple organ failure (MOF) and acute injury of lung endothelial cells. It is therefore conceivable that NE inhibitors may improve the outcome of MOF patients. A synthetic NE inhibitor, sivelestat, which was developed and released in Japan, inhibited inflammatory reactions in various animal models. We examined the medical records of patients requiring more than two days of respiratory care in four intensive care units to investigate whether sivelestat contributed to improvement of their conditions. A total of 110 patients were divided into two groups (sivelestat treated group of 57 patients and untreated group of 53 patients). The conditions and age of the patients were similar in both groups. Sivelestat (0.2 mg/kg/hr) was administered continuously for 14 days beginning on the day of the intensive care unit (ICU) admission or for less than 14 days until discharge from the ICU. Hospital mortality differed significantly between the two groups (treated: 19% and untreated: 40%, $p < 0.05$). The severity of acute lung injury is defined by the ratio of arterial oxygen partial pressure (PaO2)/fraction concentration of oxygen in the inspired air (FiO2). When the $PaO2/FiO_2$ ratio is more than 200 mmHg, the morbidity is lower. In patients with PaO2/FiO2 ratio more than 200 mmHg, the hospital mortality was 33.3% (7/21) in the untreated group and 6.0% (1/18) in the treated group ($p = 0.0236$). We conclude that administration of sivelestat reduces mortality of critically ill patients. ———— neutrophil elastase inhibitor; outcome; critically ill patient; sivelestat

Acute lung injury (ALI) results in severely impaired oxygenation (Ware and Matthay 2000) and eventually multiple organ failure (MOF). It is associated with a high mortality rate (30-60%) (Doyle et al. 1995; Zilberberg and Epstein 1998). It has been reported that the pathogenesis of ALI and MOF is based on endothelial cell injury by neutrophil elastase (NE) (Tate and Repine 1983).

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This elastase, which is released by neutrophils to kill bacteria, is an elastolytic proteinase with a broad substrate range that includes most extracellular matrix proteins (e.g., collagen, elastin, fibrin, and fibronectin) (Lee and Downey 2001). NE may injure and impair organs.

Sivelestat is a new NE inhibitor that was developed in Japan (Kawabata et al. 1991). Since sivelestat reduces pulmonary artery pressures and lung permeability (Miyazaki et al. 1998), it may reduce vascular endothelial injuries caused by release of NE from activated neutrophils and may be useful in the treatment of critically ill patients. Results of the clinical trial (Tamakuma et al. 1998) performed in Japan, suggested that sivelestat administration reduced the artificial ventilation period and duration of stay in the intensive care unit (ICU). However, there was no significant difference in hospital mortality between the sivelestat-treated group and the untreated group. We are interested in whether sivelestat affects the final outcome of critically ill patients, and therefore compared the outcomes, retrospectively by reviewing the medical records, of patients treated or untreated with sivelestat.

Subjects and Methods

Patients who received respiratory care for more than two days in ICUs, including one university hospital ICU and three city hospital ICUs, from February 2001 to June 2003 were selected. Their clinical records were retrospectively reviewed after their hospital discharge. The patients were divided into two groups (sivelestat-treated group and untreated group). There was no difference between the two groups in age and severity of their conditions. Patients were intubated and managed on mechanical ventilation by anesthesiologists. However, the decision to administer sivelestat was made by the surgeons and/or physicians of each hospital, not the anesthesiologists.

Patients who were excluded from the study included those younger than 16 years of age, pregnant women, and those with increased intracranial pressure, neuromuscular disease, or severe chronic respiratory disease.

Sivelestat (0.2 mg/kg/hr) was continuously administered for 14 days from the ICU admission day or until discharge from the ICU (i.e., less than 14 days). Ventilation with a lower tidal volume (6-7 ml/kg) and open lung approach were selected as a lung protective strategy. Organ failure and condition severity were defined by sepsis-related organ assessment score > 2 and acute physiology and chronic health evaluation (APACHE) II score. The relations between hospital and ICU mortality rates and final outcome and several parameters (the patient's age, APACHE II score, C-reactive protein [CRP], and the ratio of arterial oxygen partial pressure [PaO2]/fraction concentration of oxygen in the inspired air [FiO2]) on the day of ICU admission were examined. The severity of ALI is defined by the PaO2/FiO2 ratio. We assessed the outcome of patients whose PaO2/FiO2 ratio was more than 200 mmHg.

The data were expressed as the mean ± standard deviation (S.D.). The student's *t*-test or chi-square test was used for statistical analysis. All analyses were performed using Stat View 5.0 for Macintosh (SAS Institute Inc., Berkeley, CA, USA). The p values less than 0.05 were considered significant.

Results

The patient demographics on the day of ICU admission are shown in Table 1. There were no significant differences in the demographics between the sivelestat-treated and untreated groups. There was also no significant difference between the numbers of postoperative patients in the two groups (untreated: 27/53, and treated: 34/57). The APACHE II score of the treated group was not significantly different from that of the untreated group. There was no significant difference between the groups in the frequency of organ failures (Table 2), biochemical data, and blood gas analysis (Table 3) on the day of ICU admission. The ICU mortality rate was 25% among 110 patients: 34% in the untreated group and 16% in the sivelestat-treated group ($p = 0.0250$) (Fig. 1). The hospital mortality, representing the final outcome, was 29% among 110 patients: 40% in the untreated group and 19% in the treated group ($p = 0.0184$) (Fig. 2). In patients with PaO2/FiO2 ratio more than 200 mmHg, the hospital mortality was 33.3% (7/21) in the untreated group and 6.0% (1/18) in the treated group ($p = 0.0236$). In patients with PaO2/FiO2 ratio less than 200 mmHg, the hospital mortality was 34.4% (11/32) in the untreated group and 20.6% (8/39) in the treated group ($p = 0.1898$).

TABLE 1. *The demographic data of subjects on the ICU admission day*

	Untreated group	Sivelestat-treated group
Sex	Male 39 Female 14	Male 39 Femae 18
Age (years)	65.6 ± 15.6	65.4 ± 14.0
Height (cm)	162.3 ± 8.5	161.3 ± 8.9
Weight (kg)	59.2 ± 11.3	61.0 ± 13.8
Postoperative patients	28	23
Pneumonia	15	15
Acute pancreatitis	2	3
Sepsis	2	3
Others	8	13
APACHE II	18.7 ± 7.3	16.1 ± 6.8

Mean ± S.D.
APACHE II, acute physiology, age, and chronic health evaluation.

TABLE 2. *Organ dysfunction/failure of patients on the ICU admission day*

	Untreated group	Sivelestat-treated group
Respiratory function	92%	91%
Cardiovascular system	57%	54%
Liver function	28%	21%
Renal function	17%	32%
Bleeding of GI tract	2%	7%

TABLE 3. *The labo data of patients on the ICU admission day*

	Untreated group	Sivelestat-treated group
Temperture (°C)	37.1 ± 1.3	37.2 ± 0.9
SBP (mmHg)	123 ± 32	131 ± 36
DBP (mmHg)	58 ± 14	61 ± 18
HR (bpm)	109 ± 24	108 ± 22
RR (bpm)	20 ± 7	21 ± 8
WBC ($\times 10^3$)	12.5 ± 6.0	12.9 ± 8.7
CRP (mg/100 ml)	8.9 ± 8.0	12.7 ± 11.0
Platelet ($\times 10^4$)	21.5 ± 15.2	18.1 ± 14.3
T Bil. (mg/100 ml)	1.7 ± 1.8	2.8 ± 6.3
PaO2/FiO2 ratio (mmHg)	197 ± 106	184 ± 78
$PaCO_2$ (mmHg)	43.0 ± 17.3	41.5 ± 7.8

Mean ± S.D.
SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats/min; RR, respiratory rate; WBC, white blood counts; CRP, c-reactive protein; T Bil., total Bibirubin; PaO2/FiO2 ratio, the ratio of arterial oxygen partial pressure/fraction concentration of oxygen in the inspired air; PaCO2, arterial carbon dioxide partial pressure.

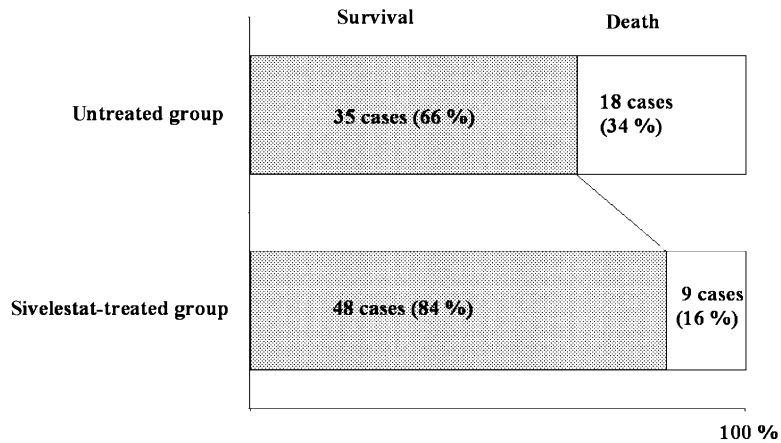

Fig. 1. The outcome at ICU.
The ICU mortality rate was 25% among 110 patients. There was a significant difference in the mortality rate between the untreated group and the sivelestat-treated group (34% vs 16%, p = 0.0250).

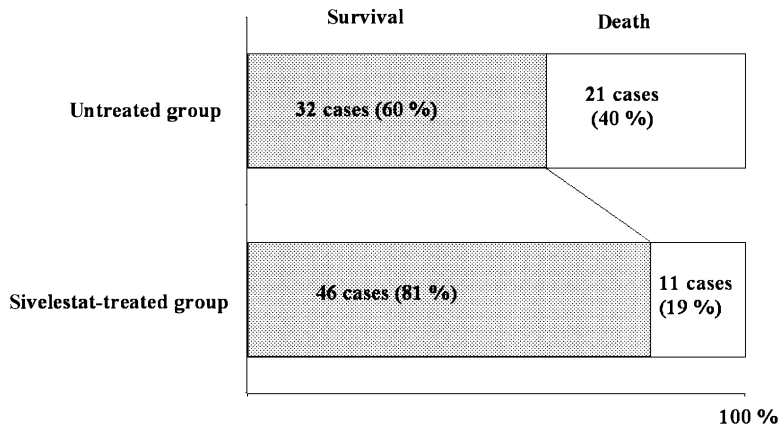

Fig. 2. The final outcome.
The values indicate hospital mortality. The hospital mortality was 29% among 110 patients. There was a significant difference in the final mortality rate between the untreated group and the sivelestat-treated group (40% vs 19%, $p = 0.0184$).

There was no significant difference between the two groups in the duration of ICU stay (untreated group: 14.9 ± 15.3 days, and treated group: 16.3 ± 14.8, p = 0.6258) and number of days on a ventilator (untreated: 8.7 ± 6.1 days, and treated: 14.6 ± 16.5, $p = 0.0319$).

The relationships between final outcome and parameters on the day of ICU admission are shown in Table 4. There was a significant difference in APACHE II score, white blood counts (WBC), and respiratory rate, but no significant difference in age, PaCO2, CRP, or PaO2/FiO2 ratio between the surviving and deceased subgroups within the two groups.

Discussion

ALI results in persistent hypoxemia, increased alveolar dead space, a further decrease in pulmonary compliance, pulmonary hypertension due to obliteration of the capillary bed (Pittet et al. 1997), and 30-60% mortality (Doyle et al. 1995; Zilberberg and Epstein 1998). The causes of deaths are mainly attributable to sepsis or multiple organ dysfunction, but not primary respiratory disorders (Le Gall et al. 1996; Ferreira et al. 2001). Therefore, multiple organ failure is a com-

TABLE 4. *The relations between the final outcome and parameters on the ICU admission day*

	Untreated group		Sivelestat-treated group	
	Survival	Death	Survival	Death
Age (years)	67.1 ± 13.3	63.4 ± 18.8	63.8 ± 14.3	72.3 ± 10.7
APACHEII	16.7 ± 6.7	21.7 ± 7.4[a]	15.2 ± 6.7	19.9 ± 5.9[b]
RR (bpm)	19.4 ± 6.3	21.8 ± 8.4	19.7 ± 7.2	24.9 ± 8.3[b]
PaCO2 (mmHg)	39.4 ± 7.0	48.3 ± 25.5	41.7 ± 8.1	40.4 ± 6.4
WBC ($\times 10^3$)	10.0 ± 5.0	16.5 ± 5.3[a]	10.9 ± 5.1	20.1 ± 13.7[b]
CRP (mg/100 ml)	8.4 ± 7.6	10.0 ± 9.0	11.5 ± 10.9	16.6 ± 11.9
PaO2/FiO2 ratio (mmHg)	198 ± 88	194 ± 131	193 ± 80	147 ± 58

Mean ± S.D.

[a] $p < 0.05$ untreated group survival.

[b] $p < 0.05$ sivelestat-treated group survival.

APACHEII, acute physiology, age, and chronic health evaluation; RR, respiratory rate; bpm, beats/min; PaCO2, arterial carbon dioxide partial pressure; WBC, white blood counts; CRP, c-reactive protein; PaO2/FiO2 ratio, the ratio of arterial oxygen partial pressure/fraction concentration of oxygen in the inspired air.

mon, devastating clinical syndrome that affects the outcome of critically ill patients with ALI in ICUs. Inflammatory cytokines released from sites of inflammation activate neutrophils, and tissue injury materials such as elastase and active oxygen are released from the activated neutrophils (Blackwell and Christman 1996; Slutsky and Tremblay 1998). NE may contribute to the development of endothelial injury and capillary permeability, which are characteristic of ALI (Suter et al. 1992). On the other hand, NE digests numerous extracellular matrix proteins (including collagen, elastin, fibrin, and fibronectin) through its broad non-specific protease function (Lee and Downey 2001).

As a result, NE can injure normal organs and play a critical role in the pathogenesis of organ failure. Improvement in the supportive treatment of ALI patients may have contributed to the recent decline reported in the mortality rate (Milberg et al. 1995; Abel et al. 1998). To reduce mortality, more effective supportive treatments for critically ill patients in addition to conventional therapies are needed. From this point of view, inhibition of NE activity can be considered as an effective treatment.

Sivelestat was discovered and developed in Japan (Kawabata et al. 1991). Sivelestat competitively inhibits neutrophil elastase activity in humans, rats, hamsters, and mice (Kawabata et al. 1991). Sivelestat can prevent elastase-dependent neutrophil migration and production of proteolysis-induced chemoattractants, but it is inactive against other proteases such as trypsin, chymotrypsin, thrombin, plasmin, kallikrein, and cathepsin G.

A double-blind, randomized study to investigate the efficacy and safety of sivelestat in 221 ALI patients was performed in Japan (Tamakuma et al. 1998). Patients were divided into a high-dose group (0.16 mg/kg/hr) and a low-dose group (0.003 mg/kg/hr). The median time until discharge from the ICU was significantly shorter in the high-dose group than in the low-dose group (16.5 vs 29 days, respectively; $p = 0.0495$). There was also a tendency toward shorter duration of mechanical ventilation in the high-dose group compared to the low-dose group (11 vs 19 days, respectively; $p = 0.0636$). However, the overall survival rate did not differ significantly between the two groups.

Intravenous sivelestat had no effect on the 28-day all-cause mortality or number of ventilator-free days in a heterogeneous acute lung injury

patient population managed with low tidal volume mechanical ventilation (Zeiher et al. 2004). In this study, there was a significant difference in hospital mortality of patients with PaO2/FiO2 ratio more than 200 mmHg (untreated; 33.3%, and treated; 6.0%, $p = 0.0236$). There was no significant difference in age between the two groups, but no one less than 50 years old died in the treated group. The results of our study suggest thought that sivelestat prevents serious illness and improves the final outcome of patients with PaO2/FiO2 ratio more than 200 mmHg.

It has been reported that the initial indexes of oxygenation and ventilation, including the PaO2/FiO2 ratio and the lung-injury score, do not predict outcomes of patients with ALI/ARDS (Luhr et al. 1999). In this study, there was no significant relation between the final outcomes and parameters on the day of ICU admission in the two groups.

Conclusion

The administration of sivelestat reduced the mortality rate of critically ill patients. In patients with PaO2/FiO2 ratio more than 200 mmHg, the degree of improvement of mortality rate was dramatic. However, further prospective studies are needed to investigate the true effect of sivelestat on the mortality rate of critically ill patients.

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