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Clinical Evaluation to Predict Effectiveness of Sivelestat Sodium Hydrate for Postoperative Acute Lung Injury by APACHE II Score

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Abstract: Sivelestat sodium hydrate (Elaspol®, Ono Pharmaceutical Co., Osaka, Japan) is a new elastase inhibitor for treating Acute Lung Injury (ALI). We studied the efficacy of sivelestat in treating postoperative ALI and compared its effectiveness between two groups of patients. The subjects were 11 patients who had undergone surgery at our hospital and received sivelestat for 5 days or longer to treat postoperative ALI. These patients were divided into a sivelestat-effective group and a sivelestat-ineffective group according to the PaO_2/FiO_2 ratio and lung injury score on the sixth day after the start of treatment. The Sequential Organ Failure Assessment (SOFA) scores, number of damaged organs, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores and C-reactive protein levels were examined in each group. Six patients were classified as the effective group and 5 patients as the ineffective group. The APACHE II score was significantly higher in the ineffective group after the second day of treatment with sivelestat and remained significantly higher until the sixth day of treatment. Our results suggest that the effects of sivelestat on postoperative ALI can be predicted through use of the APACHE II score in the early period after surgery.

Key words: Neutrophil elastase inhibitor, acute lung injury, sivelestat, APACHE II score

INTRODUCTION

A systemic inflammatory response caused by surgery commonly induces the Systemic Inflammatory Response Syndrome (SIRS) (Members of the American College of Chest Physicians, 1992). If patients with SIRS do not receive prompt, appropriate treatment, most will have multiple organ failure (Rangel *et al*., 1995). Acute Lung Injury (ALI) frequently accompanies postoperative SIRS and is difficult to treat. ALI is defined by the following: Lung injury of acute onset, hypoxemia with a PaO_2/FiO_2 of less than 300 mmHg, bilateral infiltrates on chest X-rays and the absence of signs of left-sided heart failure (not requiring measurement of pulmonary capillary wedge pressure) (Bernard *et al*., 1994). The pathological state of ALI associated with SIRS is pulmonary edema due to increased pulmonary capillary permeability and causes rapid hypoxemia. Thus, the main treatment for this condition is respiratory management with a ventilator, but there are no therapeutic agents that directly improve the lung injury.

In recent years, neutrophil elastase released from neutrophils has attracted attention as the cause of lung injury accompanying SIRS (Petty, 1991). In addition, a correlation between a rise in elastase and a decline in pulmonary function has also been reported (Idell *et al*., 1985; Donnelly *et al*., 1995). Sivelestat sodium hydrate (Elaspol®, Ono Pharmaceutical Co., Osaka, Japan) is a new drug that selectively inhibits neutrophil elastase. In clinical trials excellent results have been obtained with sivelestat with regard to the improvement in respiratory function, the length of artificial ventilation and the length of stay in the intensive care unit (Tamakuma *et al*., 2004).

Sivelestat was approved in June 2002 for use in Japan for ALI with SIRS requiring ventilatory support and has proven extremely effective.

Although many studies of Sivelestat have been done, the effectiveness of Sivelestat for postoperative ALI has not been studied. In the current study, we investigated the efficacy of Sivelestat for treating postoperative ALI and examined differences between patients in whom Sivelestat had been effective and patients in whom it had not.

MATERIALS AND METHODS

The subjects were patients who had undergone digestive surgery, respiratory surgery, neurosurgery, or orthopedic surgery at our hospital from June through December 2004. They satisfied the diagnostic criteria for

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ALI accompanying SIRS and required artificial ventilation. Respiratory disturbance due to other causes such as aspiration pneumonia was excluded. The subjects were 11 patients (8 men and 3 women; average age, 63.7 years) who had recieved sivelestat were used after surgery for 5 days or longer. They were all patients with postoperative ALI in this period admitted to our hospital, because in Japan, the effectiveness of this drug for ALI is currently recognized and it is highly improbable that the drug would not be administered to ALI patients. The subjects underlying condition were traumatic hepatosplenic injury, perforation of the colon, esophageal carcinoma, gastric carcinoma, pulmonary carcinoma, traumatic hemopneumothorax and thoracic ossification of the ligamenta flava in 1 patient each and intracerebral bleeding in 4 patients. In Japan, the administration of this drug for up to 14 days has been approved and only in artificially ventilated patients can start to use this drug. Its administration was discontinued in all patients when artificial ventilation was stopped. Even when artificial ventilation was continued, the administration was discontinued as soon as the patient was judged not to meet the diagnostic criteria for ALI. The ventilator was set in the continuous positive airway pressure mode or synchronized intermittent mandatory ventilation mode. In all patients, Positive End Expiratory Pressure (PEEP) was set at 5 cm H_2O and tidal volume at 10 m L/kg as baseline. Respiratory rate and FiO_2 were changed at optimal timing according to the patient's condition. Sivelestat was administered continuously at a dose of 0.2 mg/kg/h. No patients received corticosteroids. During the period of administration, there were no restrictions on the administration of other medications, such as antibiotics. The time from surgery to the administration of sivelestat, was within 5 h for 7 patients and 24-48 h for 4 patients. The duration of the period between the onset of ALI and the administration of sivelestat was 3 h for all patients except one (10 h). The presence of side effects was determined by abnormalities in clinical test scores at blood drawing (e.g., AST, ALT, ALP, WBC count and platelet count).

On the sixth day of sivelest treatment, all 11 patients were divided up into two groups according to the lung injury score and PaO_2/FiO_2 ratio. Patients who showed improvements in both the lung injury score and PaO_2/FiO_2 ratio from start of the treatment comprised the effective group and patients who showed no improvements comprised the ineffective group. The lung injury score was determined with the modified method of Murray *et al.* (1988) (Table 1). The number of SIRS diagnostic items before treatment, the Sequential Organ Failure Assessment (SOFA) score (Vincent *et al.*, 1996) before

Table 1: Lung injury score

Item	Score				
observed	0	1	2	3	4
PEEP (cmH_2O)	0	1-5	6-8	9-11	≥12
Pao2/FiO2	≥300	225-299	175-224	100-174	<100
Chest X-ray findings	No abnormal shadows	Abnormal shadows 1/4 sections	Abnormal shadows 2/4 sections	Abnormal shadows 3/4 sections	Abnormal shadows all 4/4 sections

The total of the score for 3 items was the lung injury score

Table 2:The background of both groups

	Effective	Ineffective	Statistics
Number of patients	6	5	
Sex (men:women)	5:1	3:2	NS
Age (Years)	62±18.5	65.8±11.7	NS
Administration period (days)	6.2±1.3	6.8±1.6	NS

Results are given as the mean±S.D.
NS = Not Significant

treatment and 2, 4 and 6 days after the start of treatment, the number of damaged organs, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (Knaus *et al.*, 1985) and the C-Reactive Protein (CRP) level of the two groups were compared. Using criteria for the SOFA score, damaged organs and systems, such as the lung, the coagulation system, the liver, the cardiovascular system, the central nervous system and the kidneys were assessed. Organs were considered damaged if the SOFA score was 2 or more. In addition, survival rates 40 days after the start of treatment were compared.

The results were presented, unless otherwise specified, as the mean±standard error. The student's t-test, repeated t-test, chi-square test and log-rank test were used as statistical tests, with $p<0.05$ indicating significance.

RESULTS

Background of the two groups: The 11 patients were divided into 6 patients of the effective group of and 5 patients of the ineffective group. The backgrounds of both groups are shown in Table 2. There were no significant differences in sex, age, or length of sivelestat treatment between the 2 groups. Results of chest XP indicated no significant differences in pulmonary infiltrates between the two groups. In addition, there was no significant difference in time from surgery to the administration of sivelestat between the 2 groups. Sivelestat was administered within 5 h post-surgery to 66% of effective cases (4/6) and 60% of ineffective patients (3/5). The PaO_2/FiO_2 ratio was less than 140 mmHg in both groups prior to treatment. On the 4th and 6th days after the start of treatment, the PaO_2/FiO_2 ratio in the effective group was significantly higher than

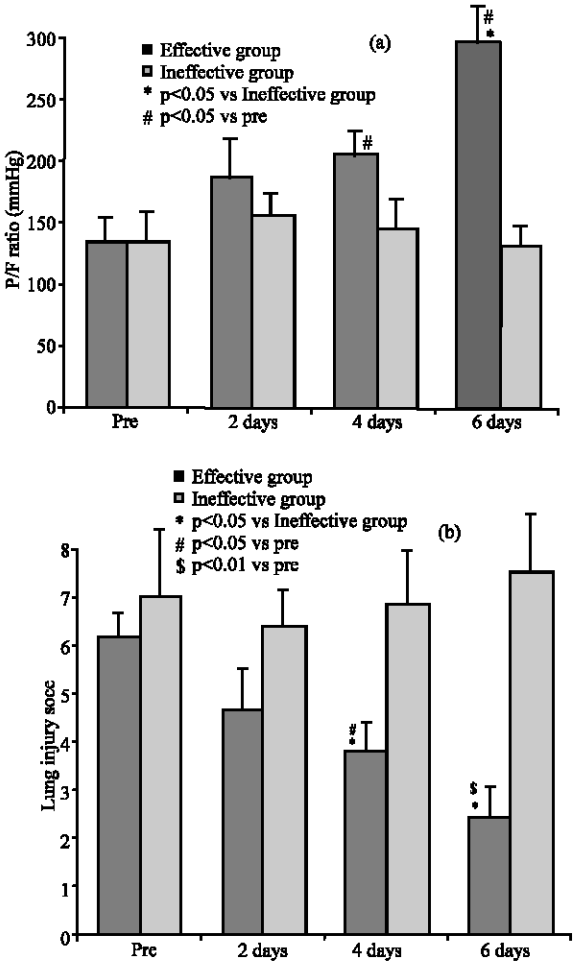

Fig. 1: PaO_2/FiO_2 ratio (a) (upper panel) and Lung injury score (b) (lower panel) in patients before treatment with sivelestat (pre) and 1, 3, 5 days after the start of treatment. Each point represents the mean value±S.E.

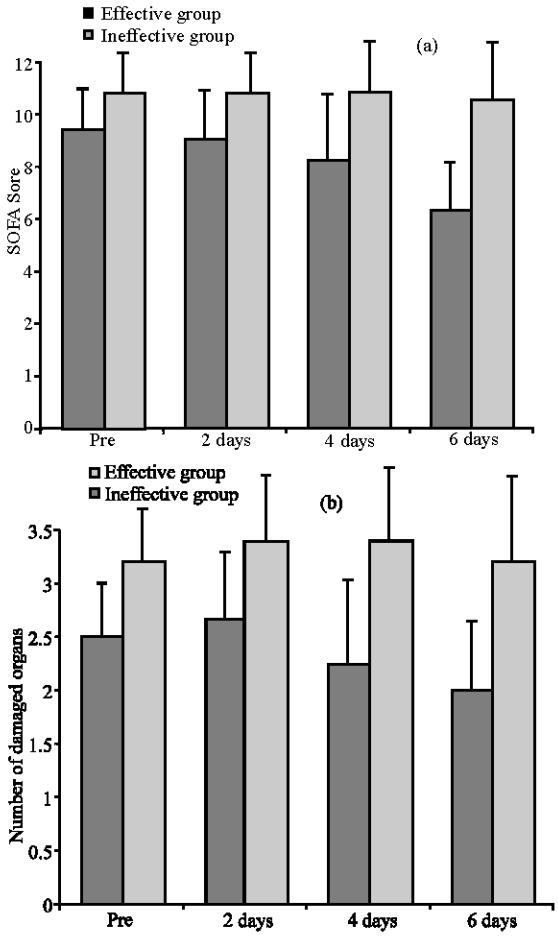

Fig. 2: SOFA score (a) (upper panel) and the number of damaged organs (b) (lower panel) in patients before sivelestat administration (pre) and 1, 3, 5 days after administration. Each point represents the mean value±S.E.

before treatment and on the sixth day was also significantly higher than that in the ineffective group (Fig. 1a). Lung injury score did not differ significantly between the groups before treatment. However, on the 4th and 6th days after the start of treatment, the lung injury score in the effective group were significantly lower than both those before treatment and the ineffective group (Fig. 1b).

Variation in CRP level: Before treatment, CRP levels tended to be higher in the effective group than in the ineffective group. The CRP level in the effective group peaked before treatment but that in the ineffective group peaked on the second day of treatment, but decreased gradually afterwards.

Number of SIRS diagnostic items: There was no significant difference between the groups in the number of SIRS diagnostic items before treatment (effective group: 2.5±0.22; ineffective group: 2.4±0.25).

SOFA score and number of damaged organs: Throughout the observation period, the SOFA score and the number of damaged organs tended to be lower in the effective group than in the ineffective group, although the differences between the groups were not significant (Fig. 2a and b).

APACHE II score: Before treatment, APACHE II score did not differ significantly between the groups. However, on the second day of treatment, the APACHE II score in the ineffective group was significantly higher than that in the effective group and remained significantly.

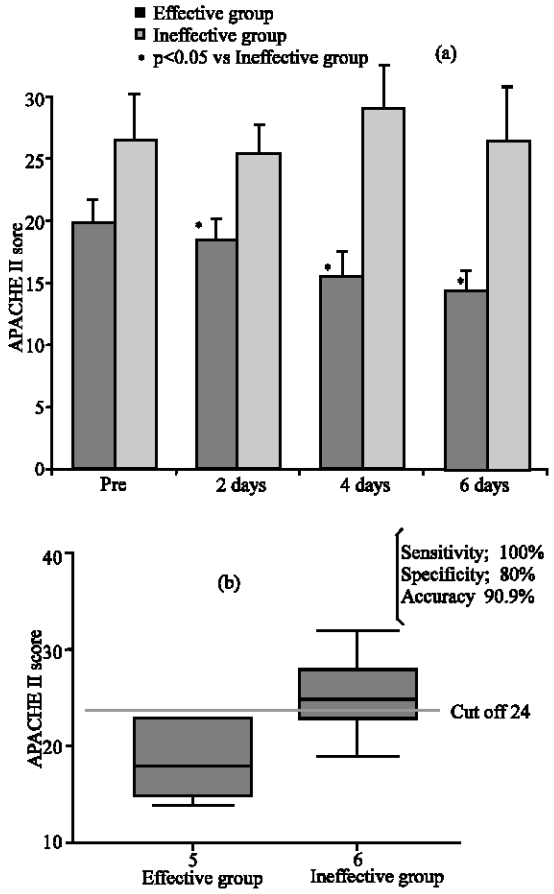

Fig. 3: APACHE II score (a) (upper panel) in patients before sivelestat administration (pre) and 1, 3, 5 days after administration. Each point represents the mean value ± S.E. APACHE II score on day 2 of treatment (b) (lower panel)

higher until the 6th day of treatment (Fig. 3a). To examine whether the effects of sivelestat can be predicted with the APACHE II score, APACHE II scores on the second day of treatment were studied. When an APACHE II score of 24 was used as the cut-off value, the sensitivity was 100% and the specificity was 80% (Fig. 3b).

Side effects: In both groups, no abnormal clinical test scores or other apparent side effects due to sivelestat were observed during administration. There were no cases in which treatment had to be discontinued.

Survival rate: Forty days after the start of treatment, the survival rate in the effective group was 83.3% (5 out of 6 patients) and only 20% (1 out of 5 patients) in the ineffective group; the survival rate was significantly higher in the effective group ($p = 0.017$).

DISCUSSION

Treatments for ALI accompanying SIRS post-surgery focus on respiratory support with a ventilator, correction of the circulating blood volume and administration of antibiotics. However, even when these treatments are appropriately performed, ALI mortality rate is still 30% (Jardin *et al*., 1999). Consequently, several protease inhibitors have been developed for the control of adverse biological responses. Murata *et al*. (1996) have found that urinastatin administered after surgery for gastric carcinoma suppresses CRP and interleukin-6 levels. In addition, Ono *et al*. (1999) have reported that after surgery for esophageal carcinoma gabexate mesilate is useful for controlling the postoperative biological response. Sivelestat is also a protease inhibitor but has an inhibitory action specific to the neutrophil elastase released by the neutrophils that are activated by inflammatory cytokines and accumulate in the lungs. A characteristic of sivelestat is that it does not act on other proteases. Thus, sivelestat is more effective for treating ALI than previously developed protease inhibitors.

The action of sivelestat has been studied in various lung injury models (Hagio *et al*., 2004; Kinoshita *et al*., 2000). In Japan, sivelestat is already used to treat postoperative ALI and has been shown to be effective. Nevertheless, treatment with sivelestat is occasionally ineffective. In phase II clinical trials, numerous damaged organs led to decreases in the survival rate (Ogawa *et al*., 1996); in phase III clinical trials, patients having four or more damaged organs were excluded (Tamakuma *et al*., 2004). In this study, the mortality rate in the ineffective group was high, because this group showed no improvement in ALI and tended to have more damage to other organs.

Whether sivelestat itself can increase the survival rate for ALI is controversial; Kadoi *et al*. (2004) reported no changes in the survival rate of patients with Acute Respiratory Distress Syndrome (ARDS) regardless of whether sivelestat was used. Conversely, Hoshi *et al*. (2005) report that hospital mortality rates for patients in critical condition who received artificial respiratory management with sivelestat administration at ICU were significantly lower in comparison to the non-sivelestat group.

Similarly, there is much debate surrounding the use of sivelestat to improve the prognosis of postoperative ALI. Previous studies reveal that ALI with no multiple organ failure improves with the use of the drug; however, postoperative ALI patients often have MOF beyond the lungs and severe acute failure of the entire body. In these cases, it is unlikely that sivelestat will effectively improve the symptoms of ALI. Furthermore, we often observed

variations in the degree of acute failure of the entire body for each postoperative ALI patient. It is therefore, difficult to determine the degree to which sivelesat alone is effective. Our data indicates that we could not predict the effectiveness of sivelestat for patients with an APACHE II score greater than 24 on the second day of administration. For ALI patients with severe failure of the entire body, we advocate treatment such as continuous hemodiafiltration which would eliminate humoral mediator more effectively at an early stage instead of continued administration of sivelestat.

Government approval documents and a report from research conducted after the drug's release indicate that the prevalence of side effects from sivelestat is 11.7%. Primary side effects include increase in AST and ALT (6.0%), increase in ALP (3.9%), increase in bilirubin (1.2%), decrease in WBC (0.8%) and increase in BUN (0.8%). Under normal circumstances, serious side effects that require discontinuation of the drug are rare. No side effects due to sivelestat were observed in any of our research participants.

In this study, it was necessary to administer sivelestat for 4 or more days, even in the effective group, to improve the P/F ratio and lung injury score. However, our findings also suggest that the medication's effects can be predicted through the APACHE II score early in treatment. A larger sample size is necessary to examine the effectiveness of sivelestat in postoperative ALI treatment. Further research is needed on the prevention of ALI when sivelestat is administered intraoperatively during extensive invasive surgery with anticipated postoperative respiratory aggravation. Effective use of sivelestat may significantly reduce postoperative ALI in the future.

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