Effect of Sivelestat Sodium Hydrate in Three Patients with Septic ARDS

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Abstract

We administered sivelestat sodium hydrate, a selective polymorphonuclear leukocyte elastase (PMNE) inhibitor, to three patients with septic ARDS. While causing a decrease in the serum PMNE and surfactant protein D levels, the neutrophil elastase inhibitor improved the PaO$_2$/FiO$_2$ ratio in all the three patients, which allowed earlier weaning of these patients from artificial ventilation. These findings suggest that sivelestat may be effective in the treatment of septic ARDS.

Introduction

In 1996, Garber et al. reviewed the risk factors of acute respiratory distress syndrome (ARDS) through a meta-analysis of 83 studies on ARDS [1]. They concluded that the most significant risk factor that consistently contributed to the development and progression of ARDS was the systemic inflammatory response syndrome (SIRS) associated with sepsis [2]. Underlying SIRS is a complex network of proinflammatory cytokines, such as the tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), and interleukin 8 (IL-8), which cause activation of neutrophils, and subsequently, when uncontrolled, multiple organ failure [3-7]. Polymorphonuclear leukocyte elastase (PMNE) released from activated neutrophils degrades connective tissue proteins of the lung, such as elastin, collagen, fibronectin and proteoglycans. PMNE also increases vascular permeability and induces the production of leukocyte chemotactic factors (e.g., C5a, IL-8). These molecular events have been demonstrated to be associated with pulmonary injury in ARDS patients. Elevated PMNE levels in the bronchoalveolar lavage (BAL) fluid have been demonstrated in ARDS patients. A significant correlation has been reported to exist between increases in the serum and BAL PMNE levels and reduced pulmonary function. In the context of these findings, we had previously suggested that surfactant protein D (SP-D) might also be involved in the pathogenesis of ARDS, because we had observed high values of this protein in ARDS patients [8,9].

Sivelestat sodium hydrate (sivelestat) is a selective PMNE inhibitor. It has been shown in experimental studies to attenuate pulmonary injury and improve respiratory function. The PMNE inhibitor has also been shown to be effective in the treatment of patients with pulmonary injury associated with SIRS [10-13]. Sivelestat was the first drug to be approved in Japan for the treatment of acute lung injury (ALI) associated with SIRS.

In this study, we administered sivelestat to 3 patients with septic ARDS and evaluated the drug’s efficacy in these patients by determining the serum PMNE and SP-D levels, as well as the PaO$_2$/FiO$_2$ (P/F) ratio.

Subjects and Methods

Table 1 shows the patient characteristics, including the primary cause of sepsis and the SIRS parameters. All the three patients were receiving antimicrobial drugs to which the isolated bacteria were sensitive. Intravenous infusion of sivelestat (Elaspol; Ono Pharmaceutical Co., Ltd., Osaka, Japan), started at the dose of 0.2 mg/kg/h within 2 hours of the diagnosis of septic ARDS, was continued for 14 days.

Sepsis was diagnosed according to SCCM/ACCP
Consensus Conference definitions for sepsis [2], and AECC criteria [14] were employed for the diagnosis of ARDS.

The serum PMNE level was measured by determining the level of the PMNE and a1 plasmin inhibitor complex (NE/a1PI complex) by enzyme-linked immunosorbent assay (ELISA) (Merck, Darmstadt, Germany); the normal range was 55 to 154 ng/ml. Serum SP-D was also quantified by ELISA (Teijin Bio Laboratories, Inc., Tokyo, Japan); the cutoff level for this parameter was 109.8 ng/ml.

Pearson’s correlation coefficient was used to analyze the relationships among the variables. P < 0.05 was considered to denote statistical significance.

Results

Figure 1 shows the clinical course of Patient 1. The time to weaning from mechanical ventilation was 324 hours. Patient 2 required 69 hours before he could be weaned off the ventilator, as shown in Figure 2. The time to weaning from artificial ventilation in Patient 3 was 266 hours, as shown in Figure 3. The relationships between the serum levels of PMNE and SP-D and the P/F ratio at individual time points during the clinical course of the three patients (Figure 1, 2, and 3) are illustrated in Figure 4, 5, and 6.

Discussion

Sivelestat was demonstrated in a lung of a model of acute lung injury, to attenuate the pathological changes characteristic of acute lung injury, such as intraalveolar bleeding, plasma protein leakage into the alveolar space, and enhanced permeability of pulmonary capillaries by reducing the protein permeability of pulmonary vascular endothelial cells and alveolar epithelial cells and by attenuating disruption of the vascular basement membrane [15, 16]. Pulmonary surfactant is a bioactive substance that is synthesized and

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**Table 1. Characteristics of three patients item of SIRS**

<table>
<thead>
<tr>
<th>case</th>
<th>age</th>
<th>sex</th>
<th>primary disease</th>
<th>BT (°C)</th>
<th>pulse rate (/min)</th>
<th>respirator rate (/min)</th>
<th>WBC (/µl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>M</td>
<td>panperitonitis</td>
<td>35.4</td>
<td>120</td>
<td>36</td>
<td>27,500</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>ileus</td>
<td>38.2</td>
<td>140</td>
<td>38</td>
<td>25,400</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>pneumonia</td>
<td>38.6</td>
<td>112</td>
<td>26</td>
<td>12,800</td>
</tr>
</tbody>
</table>

M: male, F: female, BT: body temperature, WBC: white blood cell

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![Figure 1. Clinical course of Patient 1 after the start of sivelestat infusion](image-url)
Figure 2. Clinical course of Patient 2 after the start of sivelestat infusion

Figure 3. Clinical course of Patient 3 after the start of sivelestat infusion

Figure 4. A significant correlation was observed between the serum PMNE and SP-D levels measured after the start of sivelestat therapy in all the three patients ($r = 0.811, p < 0.01$)
secreted by alveolar type II epithelial cells, that helps to prevent lung collapse at the end of expiration by reducing the surface tension at the air-water interface in the alveoli [17]. The surfactant is composed of a phospholipid component (90%), primarily consisting of saturated phospholipids and specific apoproteins (10%) containing surfactant proteins (SP)-A, SP-B, SP-C and SP-D.

SP-A and SP-D were once believed to exist only in the surfactant monolayer at the alveolar interface, and not to be released into the blood. Their clinical significance, however, has drawn increasing attention since SP-A was reported to be detected in the serum of patients with idiopathic pulmonary fibrosis and alveolar proteinosis [18,19].

We previously reported that the serum SP-D and PMNE levels were increased in ARDS patients [20]. This study further revealed a significant correlation between the serum SP-D and PMNE levels. Elevation of the serum SP-D level was attributed to possible alveolar epithelial damage by PMNE and resultant SP-D leakage into the blood. These findings indicate that PMNE not only causes direct damage of the pulmonary tissue, but also affects the metabolism and surface activities of the pulmonary surfactant, with resultant exacerbation of ARDS.

Although this study included only three ARDS patients, the results suggest that sivelestat might di-
References


