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Sivelestat treatment for acute respiratory distress syndrome in an infant

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Abstract
Resuscitation and acute cerebral damage after cardiopulmonary arrest often induce a systemic inflammatory response and subsequently cause multiple organ failure, including acute lung injury (ALI). Sivelestat has been reported to be effective for ALI associated with systemic inflammatory response syndrome (SIRS), but the effectiveness and safety of the drug for infants has not been confirmed. We report a 33-day-old infant who developed acute respiratory distress syndrome (ARDS) following hypoxic encephalopathy immediately after successful resuscitation from cardiopulmonary arrest. Sivelestat was administered continuously for 7 days with no adverse reactions, and consolidations on a chest radiograph were diminished and impaired oxygenation was markedly alleviated. Our experience suggests that intravenous sivelestat offers a new therapeutic strategy for infantile ARDS/ALI, but further investigation of the indication, administration period, and dosage is required.

Key words ARDS · Hypoxic encephalopathy · Resuscitation · SIRS · Sivelestat

Introduction

Cardiopulmonary arrest results in global ischemia, and reperfusion follows resuscitation. Systemic organ reperfusion and widespread hypoxic brain damage can subsequently trigger severe systemic inflammatory responses. Under normal circumstances, elastase from neutrophils activated by inflammatory cytokines is inhibited by endogenous agents such as α1-protease inhibitor. However, large quantities of elastase are released in severe systemic inflammatory response syndrome (SIRS), and the simultaneous release of reactive oxygen species (ROS) inactivates α1-protease inhibitor via the oxidization of methionine. Heightened elastase activity can irreversibly damage the vascular endothelial and alveolar epithelial cells of the lung [1]. Thus, severe vascular endothelial damage can result from a causal chain, leading from heightened adhesion molecule expression to neutrophil activation [2], to heightened levels of neutrophil elastase and thrombomodulin [3]. A study in animals indicated that interleukin (IL)-6 levels reached maximum levels in serum and cerebrospinal fluid after several hours following cerebral ischemia, and after several days in brain tissue [4]. Furthermore, hypoxic brain injury in infants leads to increased proinflammatory cytokines in the cerebrospinal fluid (CSF) and plasma [5]. These findings suggest that global ischemia, including cerebral ischemia, rapidly induces high cytokine levels systemically. Indeed, Audebert et al. [6] reported positive correlations between the magnitude of systemic inflammatory reactions, cerebral stroke volumes, and the severity of neurological impairments.

Sivelestat is a drug that was recently developed in Japan for the selective inhibition of neutrophil elastase. Sivelestat is not inactivated by ROS [7] and is an effective treatment for acute lung injury (ALI) associated with SIRS in adults [8]. We report the first known clinical administration of sivelestat to an infant. Sivelestat was an effective treatment for ARDS following hypoxic encephalopathy after resuscitation in a 33-day-old boy.

Case report

The patient was a male infant born at 40 weeks and 2 days of gestation with a body weight of 3420 g, without any apparent perinatal abnormality. At the age of 33 days, his mother (a nurse) noticed facial pallor and cardiopulmonary arrest while the patient was sleeping at home in the supine position. She immediately initiated cardiac massage and called an ambulance. On arrival

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at the hospital, the infant was unable to move his body, open his eyes, or cry, and he presented with complete cardiopulmonary arrest and cyanosis. However, light reflexes and miosis were noted. Heartbeat resumed 10 min after the initiation of resuscitation. Computed tomography (CT) indicated damage to the basal nuclear region and hypothalamus, as well as an indistinct boundary between the cortex and medulla. Coupled with generally low brainwave potentials, the CT evidence strongly suggested hypoxic encephalopathy. Other organs did not show abnormality.

Immediately after intubation, he was ventilated with volume-controlled ventilation (VCV), fractional inspired oxygen ($F_{I_{O_2}}$) of 1.0, positive end-expiratory pressure (PEEP) of 5 cmH_2O, and tidal volume of 10 ml kg^{-1}, and his Pa_{O_2} increased to 412 mmHg. The ventilator mode was changed to pressure-controlled synchronized intermittent mandatory ventilation (SIMV) plus pressure support (PS). However, hypoxemia accompanied by labored breathing and tachypnea developed 30 min after his admission to the intensive care unit (ICU). In response, the ventilator mode was changed to pressure control ventilation (PCV) with a PEEP of 15 cmH_20 under continuous anesthesia with midazolam and vecuronium. Six hours after his ICU admission, the white blood cell count had decreased markedly, from 12 400 cells/ mm^3 before admission to 1800 cells/mm^3 (Fig. 1). A chest radiograph detected rapid bilateral expansion of an infiltration shadow (Fig. 2A). Simultaneously, pulmonary compliance

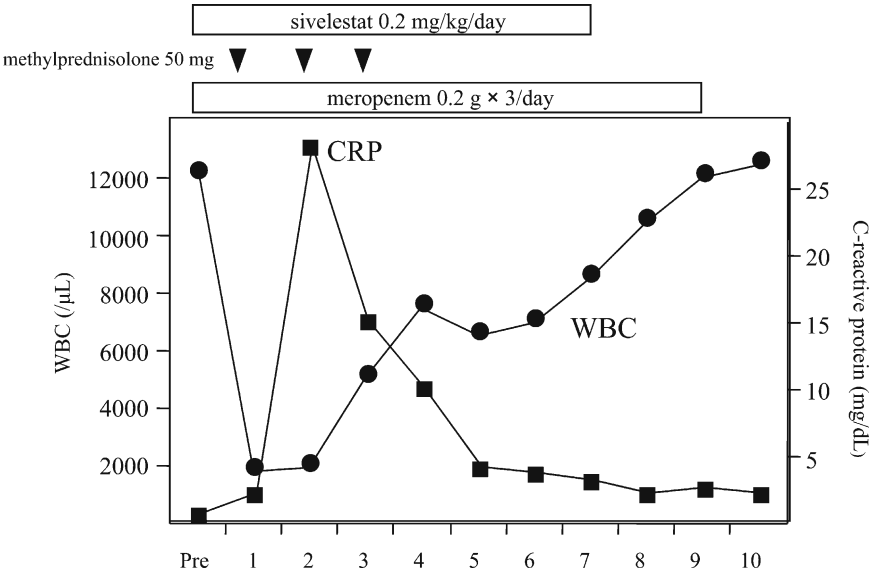

Fig. 1. Changes in C-reactive protein (CRP) levels and WBC counts before and after sivelestat administration

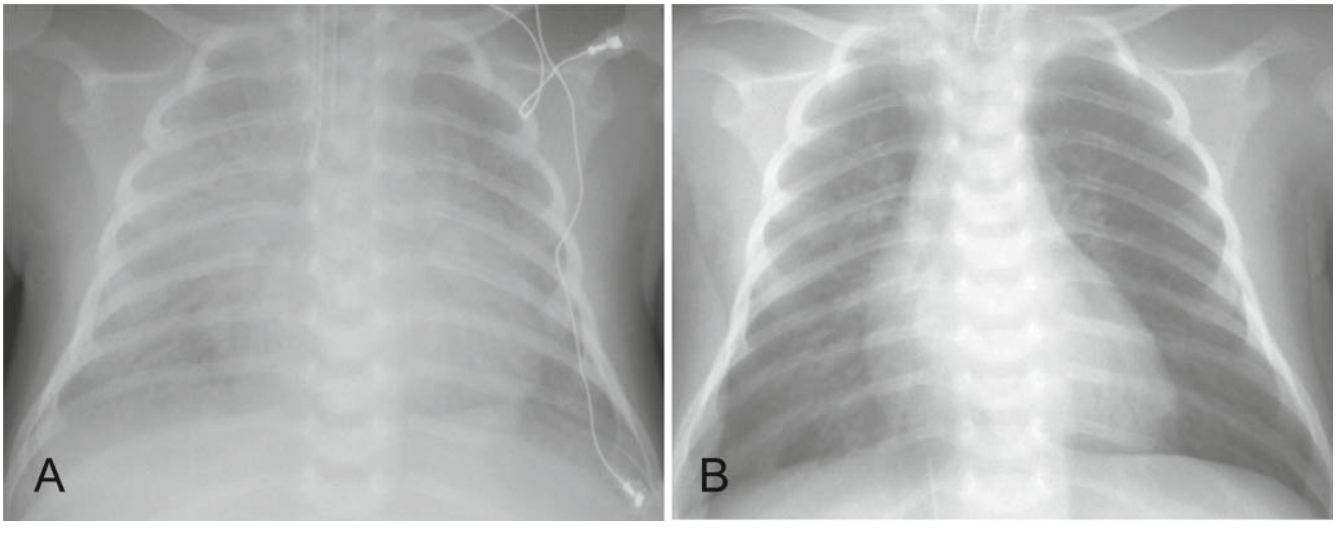

Fig. 2A,B. Radiographic findings in the infant patient following intensive care unit (ICU) admission. **A** Posterior-anterior chest X-ray revealed consolidations in bilateral lung fields following rapid leukopenia and a reduction in the oxygenation index. **B** Consolidation shadows were diminished on day 7, and sivelestat infusion was discontinued

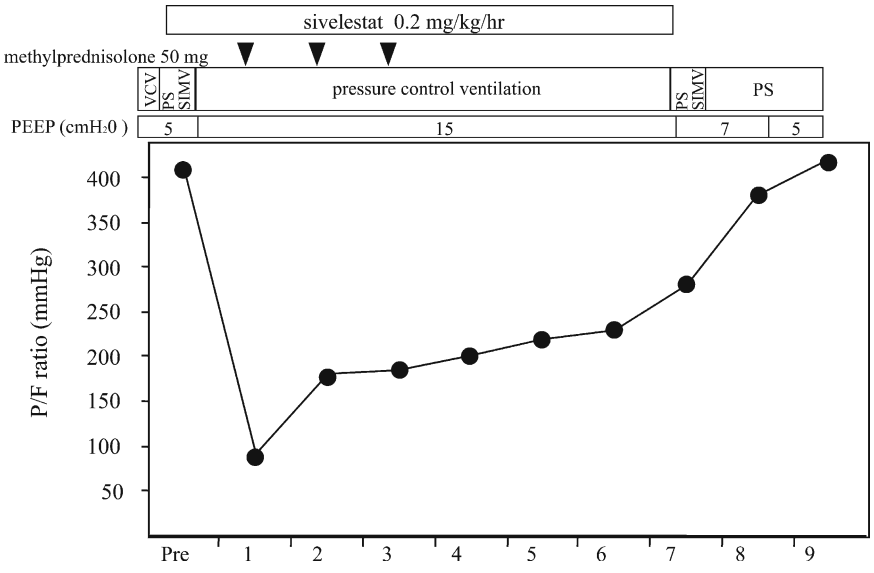

Fig. 3. Changes in the Pa_{O_2}/fractional inspired oxygen ($F_{I_{O_2}}$) (P/F) ratio before and after sivelestat administration. *PEEP*, Positive end-expiratory pressure; *VCV*, volume-controlled ventilation; *PS*, pressure support; *SIMV*, synchronized intermittent mandatory ventilation

decreased rapidly, and Pa_{O_2} decreased to 63.4 on $F_{I_{O_2}}$ 0.7 (P/F ratio = 90.5; Fig. 3).

Because echocardiography did not detect cardiac failure, the patient was diagnosed with ARDS induced by excessive pulmonary accumulation of activated neutrophils following SIRS. Immediate continuous infusion of sivelestat (0.2 $mg \cdot kg^{-1} \cdot h^{-1}$) was initiated, and methylprednisolone was administered as one bolus dose of 50 mg every 24 h. To prevent severe infection because of corticosteroid-induced immunosuppression, meropenem was administered until extubation. All bacterial cultures were negative for the duration of treatment. Oxygenation and pulmonary compliance were not improved by placing the patient in the prone resting position, and pneumomediastinum and consolidations were noted on a chest radiograph taken on ICU day 2. Methylprednisolone administration was discontinued on day 3 due to marked depression of inflammatory reaction, whereas sivelestat infusion was continued because chest radiographic findings, the P/F ratio, and pulmonary compliance did not show signs of improvement. Subsequently, oxygenation improved gradually (Fig. 3) and vecuronium infusion was discontinued on day 6. A marked decrease in consolidations was noted on day 7 (Fig. 2B), and midazolam and sivelestat infusions were discontinued. The patient was weaned gradually from the ventilator and extubated on ICU day 9 (Fig. 3).

Discussion

Several hours after resuscitation, our infant patient exhibited marked leukopenia, impaired oxygenation, and a ground-glass appearance in the bilateral lungs. Cardiopulmonary resuscitation may have induced a marked systemic inflammatory response. It is possible that the inflammatory response led to heightened neutrophil activation, and concomitant accumulation in the lung may have been responsible for the injury. In response, we administered sivelestat at a dose of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ continuously for 7 days. This treatment regimen was consistent with the standard use of this drug in adult patients. Major side effects such as liver dysfunction or thrombocytopenia did not develop. In this patient, high doses of methylprednisolone were administered to control an excessive systemic inflammatory response. Due to marked depression of C-reactive protein (CRP) levels after 3 days and a risk of severe infection because of the immunosuppression [9], methylprednisolone was subsequently discontinued. In contrast, sivelestat does not affect phagocytosis, ROS production, or the bactericidal activity of neutrophils in vitro [7].

The sivelestat trial in ALI patients requiring mechanical ventilation (STRIVE) study reported by Zeiher et al. [10] indicated that sivelestat was ineffective for patients with ALI who received invasive mechanical ventilation within 48 h of symptom onset. However, some complications call these results into question, including variability in the time from onset of ALI to the start of sivelestat infusion and the fact that many of the patients also suffered from multiple organ failure. In contrast, our patient was diagnosed with ALI soon after symptom onset and did not develop multiple organ failure, permitting the immediate administration of sivelestat. Though the evidence in infants is not established, consideration of the mechanism of its drug action indicates that sivelestat should be administered as early as possible, before irreversible lung injury develops.

Furthermore, the hypercytokinemic state following resuscitation-related hypoxic encephalopathy is often transient, unlike that in severe infectious disease. Thus, it is possible that rapid treatment after resuscitation is particularly critical, such that the potential for irreversible damage to the lungs and multiple organ failure can be reduced during the transient period of hypercytokinemia.

In conclusion, we found that SIRS-associated ALI developed following hypoxic encephalopathy after resuscitation in an infant. We emphasize the critical importance of the early diagnosis of ALI via adequate monitoring in the ICU, and the need for rapid treatment for similar patients. Experience with our patient suggests that continuous intravenous sivelestat can be used to effectively treat infantile ARDS/ALI with no adverse drug reactions, but additional investigation of the indication, administration period, and appropriate dosage is required.

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