Intrathoracic Administration of OK-432 Elevates the Serum Procalcitonin Levels

Takashi Ogasawara, Hiroki Umezawa, Shinpei Kato, Toshiaki Yano, Norio Kasamatsu and Ikko Hashizume

Abstract

Objective  The intrathoracic administration of OK-432, a lyophilized preparation of the heat- and penicillin-treated Su-strain of type 3, group A Streptococcus pyogenes, is performed in Japan for pleurodesis of malignant pleural effusion or pneumothorax. Persistent fever is often observed after pleurodesis. To elucidate whether procalcitonin (PCT) is useful for distinguishing between the side effects of OK-432 and infection, we measured the serum PCT levels before and after pleurodesis.

Methods  We performed a prospective study of 12 patients with refractory pleural effusion or pneumothorax who required pleurodesis using OK-432 between August 2011 and February 2012. The serum PCT and C-reactive protein (CRP) levels were measured on days 1 and 3.

Results  Of the 12 patients, five had pneumothorax and seven had uncontrolled pleural effusion with carcinomatous pleurisy. The median serum levels of PCT and CRP increased from 0.055 to 1.59 ng/mL (p = 0.0022) and from 1.52 to 16.82 mg/dL (p = 0.0022), respectively. The fevers subsided without antibiotic administration.

Conclusion  The serum PCT level may not be useful for distinguishing fever caused by side effects of OK-432 from that caused by bacterial infection. The intrathoracic administration of OK-432 increased the serum levels of both PCT and CRP in the absence of any bacterial infection.

Key words: OK-432, procalcitonin, pleurodesis, C-reactive protein


Introduction

OK-432 (Picibanil®, Chugai Pharmaceutical Co, Ltd, Tokyo, Japan) is a lyophilized preparation of the heat- and penicillin-treated Su-strain of type 3, group A Streptococcus pyogenes. The standard treatment for symptomatic and refractory pleural effusion is pleurodesis achieved with the intrathoracic administration of chemical agents. In Japan, OK-432 is widely used to treat malignant pleural effusion, chylothorax, pneumothorax and so on (1-3). The side effects of pleurodesis with OK-432 are fever and chest pain. After pleurodesis, persistent fever is sometimes observed without the use of anti-pyretics and the serum C-reactive protein (CRP) level increases; hence, it is difficult to distinguish between pleural infection and the side effects of OK-432 treatment. Unnecessary antibiotic administration may therefore sometimes be started in order to treat persistent fevers.

Procalcitonin (PCT) is a diagnostic marker of severe bacterial infection and sepsis. The ubiquitous release of PCT during infection is induced directly by microbial toxins and/or indirectly by humoral factors (e.g. interleukin [IL]-1β, IL-6 and tumor necrosis factor [TNF]-α) or cell-mediated host responses (4). PCT-controlled antibiotic therapy leads to important reductions in antibiotic use in patients with lower respiratory tract infections without increasing the risk for serious adverse outcomes (5). We experienced a few cases of persistent fever after pleurodesis with OK-432 in which the serum levels of PCT increased. According to PCT guidelines, we administered antibiotics without any evidence of bacterial infection. However, it is questionable whether antibiotic administration is necessary, and it is unclear how the
serum PCT level changes during OK-432 therapy. The aim of this study was therefore to elucidate whether PCT is useful for distinguishing between OK-432-induced fever and complicated infections after pleurodesis.

## Materials and Methods

We conducted a prospective study of patients with refractory pleural effusion or pneumothorax who received the intrathoracic administration of OK-432 at the Hamamatsu Medical Center between August 2011 and February 2012. The Institutional Review Board at our hospital approved the study and all patients provided their informed written consent.

All patients were hospitalized and underwent chest tube drainage. The patients received intrathoracic injections of OK-432 at a dose of 5 or 10 Klinische Einheit (KE) with or without 100 mg of minocycline. The selection of the dose of OK-432 was left to the discretion of the treating physician. The levels of serum PCT and CRP were measured on day 1 (before treatment) and day 3 of pleurodesis with OK-432. In this study, we did not assess the success or failure of pleurodesis, the serum PCT level may not be useful for distinguishing between the presence of a complicated infection and fever as a side effect of OK-432 treatment.

For patients who experience persistent fevers after OK-432 administration of OK-432 elevates the serum levels of PCT in 0.19 to 5.01 ng/mL; median, 0.05 to 1.59 mg/dL; p=0.0022, and CRP: mean, 2.47 to 17.6 mg/dL; median, 1.52 to 16.82 mg/dL; p=0.0022, respectively) (Figure). No significant relationships were observed between the doses of OK-432 or the combination effect of minocycline and the increases in the PCT levels (Table 3).

## Discussion

This is the first study to show that the intrathoracic administration of OK-432 elevates the serum level of PCT in patients with malignant pleural effusion or pneumothorax. For patients who experience persistent fevers after OK-432 pleurodesis, the serum PCT level may not be useful for distinguishing between the presence of a complicated infection and fever as a side effect of OK-432 treatment.

OK-432, a preparation of inactivated Streptococcus pyogenes used to treat malignant pleural effusion in Japan, was originally developed as an immunotherapy agent for cancer. OK-432 is well known to induce interferon (IFN-γ) production, thus resulting in the induction of activated natural kil-

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td></td>
<td>10</td>
<td>2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline disease</th>
<th>Pneumothorax</th>
<th>Refractory pleural effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5</td>
<td>4</td>
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</table>

The patient characteristics are summarized in Table 1. Between August 2011 and February 2012, 12 patients were enrolled in this study. The median age of the patients was 74.5 years. Of the patients, 10 were men and two were women. Five patients with pneumothorax were not regarded as operable because of severe chronic obstructive pulmonary disease (COPD) or chronic respiratory failure. Of the seven patients with refractory pleural effusion, four had carcinomatous pleurisy due to non-small cell lung cancer (adenocarcinoma), one had pleural effusion with malignant mesothelioma, one had yellow nail syndrome and one had pleural effusion of unknown origin despite repeated thoracentesis. The final patient did not want to undergo thoracoscopy due to old age, and pleurodesis with OK-432 was performed to relieve her dyspnea.

Eight patients received 5 KE of OK-432 into the thoracic cavity as pleurodesis, while the other four patients received 10 KE (Table 2). Minocycline was used concurrently in six of 12 patients. All patients had episodes of fever and the median maximum body temperature was 38.7°C. Body temperatures decreased after an average of 2.75 days without any antibiotic administration.

The serum levels of both PCT and CRP increased significantly two days after pleurodesis with OK-432 (PCT: mean, 0.19 to 5.01 ng/mL; median, 0.055 to 1.59 mg/dL; p=0.0022, and CRP: mean, 2.47 to 17.6 mg/dL; median, 1.52 to 16.82 mg/dL; p=0.0022, respectively) (Figure). No significant relationships were observed between the doses of OK-432 or the combination effect of minocycline and the increases in the PCT levels (Table 3).
Administeration of OK-432 in patients with malignant pleural cells (6). However, the mechanism of action of OK-432 during pleurodesis remains unclear. The intrathoracic administration of OK-432 in patients with malignant pleural effusion induces the production of neutrophil chemotactic factors (IL-8 and C5a) and cytokines (IL-1β and IL-6); therefore, neutrophils are the first cells to infiltrate the pleural cavity (7). OK-432 is also used for sclerotherapy of lymphatic malformations in head and neck lesions and various cystic lesions of the neck (8-10). After undergoing OK-432 sclerotherapy, patients show clinical manifestations of inflammation such as local tenderness, swelling, erythema and fever (8). OK-432 induces the production of IL-6, IFN-γ and TNF-α in murine splenocytes (11). These cytokines are similarly detected in lymphatic malformation lesions that occur following OK-432 injection (9). Therefore, following the initial infiltration of neutrophils, activated monocytes accumulate in the pleural cavity and various cytokines and chemokines, including IL-6, IL-8, IFN-γ, TNF-α, monocyte chemotactant protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α/β, are secreted (7, 12). These cytokines contribute to the sclerosing effects of OK-432 treatment. These inflammatory responses are reflected at the systemic level, i.e. synthesis of CRP by hepatocytes is induced (10, 13).

Numerous studies support the high diagnostic reliability of PCT for diagnosing sepsis and severe bacterial infections. PCT is released from parenchymal cells following stimulation of proinflammatory cytokines, e.g. IL-1β, IL-6 and TNF-α (4). Although circulating monocytes hardly produce any PCT after stimulation with high concentrations of endotoxins (14, 15), the adhering monocytes exhibit significant PCT production. According to the results of in vitro and/or ex vivo experiments, direct contact of adherent monocytes with parenchymal cells leads to the production of PCT (16-18). The detailed mechanism underlying PCT production after OK-432 pleurodesis remains unclear and, thus, warrants further examination.

Other situations in which PCT production can be induced without evidence of bacterial infection have been reported. The serum PCT levels may be very high in patients with inhalational injuries, burn injuries, pancreatitis, severe trauma, heart attack or stroke and those who undergo extensive surgery (19). Both the translocation of lipopolysaccharides (LPS) and/or other bacterial products from the gut to the systemic circulation and high concentrations of proinflammatory cytokines in plasma may result in elevated PCT levels (20). The experimental administration of LPS to healthy volunteers induces marked and prolonged elevations of the serum PCT levels (21, 22). Injection of high-dose TNF-α also induces elevations of the PCT levels along with the levels of other proinflammatory proteins (23). Elevation of the serum PCT levels after intrathoracic administration of OK-432 is induced through both translocation of OK-432 itself and increased levels of proinflammatory cytokines in plasma.

In patients with sepsis, PCT levels of 0.5 to 2 ng/mL are often observed. In the present study, the PCT levels increased to >0.5 ng/mL in 10 of 12 patients (83%); however, bacterial infections were not observed. In cases with viral infections, the PCT levels are generally not increased because the production of IFN-γ induced during viral infections is considered to inhibit the production of PCT (4). Although the IFN-γ levels are significantly elevated in aspirates obtained from lesions that develop after OK-432 sclerotherapy (in the investigation of lymphatic malformations) (9), no systemic increases in the serum IFN-γ levels are detected (10). The production of PCT may not be reduced by IFN-γ induced locally in the pleural cavity; hence, the serum PCT level is significantly elevated after OK-432 pleurodesis.

Our analysis has several significant limitations. First, the patient group was comprised of a heterogeneous population with various diseases, including malignant pleural effusion, non-malignant pleural effusion and pneumothorax. The present results need to be confirmed in a uniform patient background. Second, both the selection of the dose of OK-432 and the decision to administer the combination with or without minocycline were left to the treating physician. However, no significant relationships were observed between the doses of OK-432 or the combination effect of minocycline and the changes in the PCT levels. Third, in the present study, no patients experienced infection events. We were therefore unable to assess the serum levels of PCT in pa-

<table>
<thead>
<tr>
<th>Laboratory findings, median (range)</th>
<th>(n = 12)</th>
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<tbody>
<tr>
<td>Procalcitonin (ng/mL)</td>
<td>0.055 (0.02-1.68)</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>1.52 (0.03-7.17)</td>
</tr>
<tr>
<td>Dose of OK-432, No. (%)</td>
<td></td>
</tr>
<tr>
<td>5 KE</td>
<td>8 (67)</td>
</tr>
<tr>
<td>10 KE</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Minocycline, No. (%)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Fever, median (range)</td>
<td></td>
</tr>
<tr>
<td>Maximum (°C)</td>
<td>38.7 (37.6-39.4)</td>
</tr>
<tr>
<td>Duration of fever (days)</td>
<td>2.5 (1-6)</td>
</tr>
</tbody>
</table>

**Figure.** Changes in the serum PCT and CRP levels before and two days after OK-432 pleurodesis. The PCT levels are represented by the logarithmic scale.

**Table 2. Clinical Features**

The authors state that they have no Conflict of Interest (COI).

### References


Table 3. Relationship between Differences in the Serum PCT Levels and the Doses of OK-432 or Minocycline

<table>
<thead>
<tr>
<th>Dose of OK-432 or Minocycline</th>
<th>Difference of PCT level [ng/mL, median (range)]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 12)</td>
<td>1.54 (0.14-21.2)</td>
<td></td>
</tr>
<tr>
<td>OK-432 (n = 12)</td>
<td>5 KE</td>
<td>1.97 (0.14-11.0)</td>
</tr>
<tr>
<td>Minocycline (n = 12)</td>
<td>none</td>
<td>2.17 (0.14-21.2)</td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>1.34 (0.23-8.65)</td>
</tr>
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</table>

Patients with bacterial infections that developed after pleurodesis with OK-432. We performed no culture tests, e.g. cultures of the pleural effusions or the tips of the chest tubes. Nevertheless, we monitored the clinical course of each patient without antibiotic administration in the absence of bacterial infection. Although our findings suggest that PCT measurement may only be of limited effectiveness in making the differential diagnosis of infection, careful follow-up of a patient’s clinical course and aggressive culture testing should be required to distinguish bacterial infections from side effects of OK-432 for pleurodesis. Fourth, this study was a single center trial of a small number of patients at a community hospital. There are only a few reports of the incidence rate of infection events occurring after OK-432 pleurodesis. According to preliminary data, we expected the incidence rate of infection and to validate the usefulness of PCT as a marker of bacterial infection.

In conclusion, the intrathoracic administration of OK-432 significantly increases the serum PCT levels in the absence of bacterial infection. Although the mechanisms underlying the actions of OK-432 remain unclear, this observation suggests that PCT may not be useful for distinguishing between fever as the side effects of OK-432 treatment and fever due to a complicated bacterial infection.

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