Analgesic-induced Asthma Caused by 2.0% Ketoprofen Adhesive Agents, But Not by 0.3% Agents

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Abstract

A 74-year-old woman was admitted with an asthma attack. She had a 40-year history of sinusitis, nasal polyp and analgesic-induced asthma; however, asthma had never occurred when she used a 0.3% ketoprofen adhesive patch (Mohrus®) for stiff shoulder or lumbago. In the hospital, a life-threatening asthma attack suddenly occurred two and a half hours after application of a 2.0% ketoprofen adhesive tape (Mohrus tape®) to her shoulder. She was treated with bronchodilator and glucocorticoid and extubated after 20 hours. A drug lymphocyte stimulating test (DLST) was strongly positive for ketoprofen. We suspected that drug-induced hypersensitivity coexisted in the present case, but it was not clear whether or not the hypersensitivity was related to the pathogenesis of analgesic-induced asthma. (Internal Medicine 40: 124-126, 2001)

Key words: life-threatening diseases, transdermal absorption, challenge and patch tests, drug lymphocyte stimulating test (DLST), maximal concentration (C\text{max}), time to maximal concentration (T\text{max})

Introduction

The drugs most commonly associated with acute induction of asthma are nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin, coloring agents such as tartrazine, beta-adrenergic antagonists and sulfiting agents (1). Approximately 1–10% of patients with bronchial asthma are potentially susceptible to analgesic-induced asthma, also known as "aspirin-induced asthma" (2–4). Recently, there have been a few reports in which transdermal absorption type NSAIDs (ketoprofen) adhesive patches or skin lotion, have led to aspirin-induced asthma (5, 6). While the mechanism by which NSAIDs elicit bronchospasms is not clear, immediate hypersensitivity does not seem to be involved (1). The present report describes a case of aspirin-induced asthma due to 2.0% ketoprofen adhesive tapes.

Case Report

A 74-year-old non-smoking woman was admitted with a moderate attack of bronchial asthma on September 24, 1999. She had a 40-year history of sinusitis, nasal polyp and bronchial asthma induced by administration of NSAIDs, but analgesic-induced asthma had never occurred when she used 0.3% ketoprofen adhesive agents (Mohrus®, Hisamitsu Pharmaceutical Co., Inc., Saga) for stiff shoulder or lumbago. On admission, her body temperature was 36.2°C, heart rate 92 beats/min, respiratory rate 20/min, and blood pressure 107/81 mmHg. Analysis of arterial blood showed a hypoxemia and hypercapnia (pH 7.46, PaO\text{2} 58.8 Torr, PaCO\text{2} 31.9 Torr, HCO\text{3} - 24.8 mmol/l). Laboratory data revealed a white blood cell count of 7,900/mm\text{3}, red blood cell count 475x10\text{4}/mm\text{3}, hemoglobin 14.4 g/dl, platelet count 31.5x10\text{4}/mm\text{3}, aspartate aminotransferase 122 U/l, alanine aminotransferase 128 U/l, lactate dehydrogenase 288 U/l, alkaline phosphatase 149 U/l, C-reactive protein 0.1 mg/dl, IgE 178 U/ml, and anti-HCV antibody 93.4. The patient was given 500 mg of aminophylline and 200 mg of hydrocortisone sodium succinate intravenously for six days in addition to administration of 400 mg theophylline and 20 mg prednisolone per day, of which the latter was tapered to 5 mg per week. Her symptoms subsided completely within two weeks. She often used 0.3% ketoprofen adhesive patches for stiff shoulder or lumbago.

When still in hospital, she had applied a 2.0% ketoprofen adhesive patch (Mohrus tape®, Hisamitsu Pharmaceutical Co., Inc., Saga) to her shoulder at 3:00 PM on October 5, 1999, but stripped it off at 4:00 PM because she felt a burning pain on the shoulder. There were no skin reactions associated with immediate-type hypersensitivity. At 5:30 PM, she had a sudden onset of severe dyspnea and became unconscious requiring mechanical ventilation, with urinary and fecal incontinence. Analysis of arterial blood showed severe hypoxemia and hypercapnia (pH 7.03, PaO\text{2} 50.1 Torr, PaCO\text{2} 118.9 Torr, HCO\text{3} - 28.9 mmol/l). Chest roentgenogram on intubation showed no abnormality (Fig. 1). She was extubated after 20 hours to im-
prove arterial blood gas by treatment with 500 mg of aminophylline and 400 mg of hydrocortisone sodium succinate intravenously. Challenge and patch tests were not performed because adhesive agents had led to a life-threatening asthma attack. A drug lymphocyte stimulating test (DLST) was strongly positive for ketoprofen. In addition, the results were also positive for oxybenzone and rosin glycerin ester, which are additives in ketoprofen adhesive agents (Table 1).

**Discussion**

Analgesic-induced asthma is a life-threatening condition. It has been reported that this disease accounts for 20% of near-death attacks in asthma (4) and 8% of asthma attacks requiring mechanical ventilation (7). Indomethacin, fenoprofen, naproxen, ibuprofen and mefenamic acid are related to analgesic-induced asthma. Ketoprofen, which is a 2-(3-benzoylphenyl) propionic acid, had also been reported to be related to this condition 20 years ago (8). The renal contribution to the plasma clearance of free ketoprofen is thought to be about 10% and ketoprofen is excreted via urine as a form of ketoprofen glucuronide (9). In addition to oral, intramuscular and rectal administration, transdermal absorption type ketoprofen adhesive patches or skin lotion have become known to be related to analgesic-induced asthma. As noted in the article by Tanaka et al (5), Miyairi et al were the first to report, in 1990, a case of analgesic-induced asthma due to transdermal absorption-type ketoprofen ointment. To the best of our knowledge, there have been two reports in which ketoprofen adhesive patches or skin lotions, have led to analgesic-induced asthma. In one report a 40-year-old woman had a life-threatening asthma attack 5 hours after use of a ketoprofen adhesive patch (5) and in the other a 40-year-old woman had an attack of asthma 3 hours after application of ketoprofen lotion on skin (6). In the present case, although she felt a burning pain on the shoulder and stripped off the ketoprofen adhesive agents one hour later, she had a severe asthma attack requiring mechanical ventilation after a further 90 minutes. The 3–5 hour interval is characteristic of analgesic-induced asthma after the use of transdermal absorption-type NSAIDs agents.

It is especially noteworthy that a life-threatening asthma attack in this case was induced by 2.0% ketoprofen adhesive agents, but not by 0.3% agents. The maximal concentration ($C_{\text{max}}$) and time to maximal concentration ($T_{\text{max}}$) of ketoprofen in serum when 0.3% ketoprofen adhesive patches were used on the back were 43.1 ng/ml and 12 hours. $C_{\text{max}}$ and $T_{\text{max}}$ of 2.0% ketoprofen adhesive agents were 135.9 ng/ml and 12.7 hours (unpublished data). Tanaka et al (5) reported that serum

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**Figure 1.** Chest roentgenogram on intubation showed no abnormality.

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**Table 1. Drug Lymphocyte Stimulating Test (DLST) for Ketoprofen and Additives in 0.3% and 2.0% Ketoprofen Adhesive Patches**

<table>
<thead>
<tr>
<th></th>
<th>0.3% ketoprofen adhesive agent</th>
<th>2.0% ketoprofen adhesive agent</th>
<th>Stimulation index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoprofen</td>
<td>☐</td>
<td>☐</td>
<td>*797</td>
</tr>
<tr>
<td>L-menthol</td>
<td>☐</td>
<td>☐</td>
<td>155</td>
</tr>
<tr>
<td>Oxybenzone</td>
<td>☐</td>
<td>☐</td>
<td>*198</td>
</tr>
<tr>
<td>Dibutylhydroxytoluene</td>
<td>☐</td>
<td>☐</td>
<td>150</td>
</tr>
<tr>
<td>Rosin ester</td>
<td>☐</td>
<td>☐</td>
<td>*209</td>
</tr>
</tbody>
</table>

*A A stimulation index of more than 180% is positive.
ketoprofen levels on the occasion of severe attacks (81.7 ng/ml) were higher than after use of 0.3% ketoprofen adhesive agents (Miltax®, Daiichi Pharmaceutical Co., Ltd., Saitama) in healthy volunteers. We could not collect blood samples to measure the levels during severe attack. However it is possible to speculate that the difference between serum ketoprofen levels when using 0.3% and 2.0% adhesive agents is related to whether or not analgesic-induced asthma occurs. In addition, there were no skin reactions associated with immediate-type hypersensitivity. Those facts confirmed that analgesic-induced asthma is a dose-dependent disease and is not only related to immediate-type hypersensitivity.

On the other hand, it has been reported that the effect of NSAIDs, including ketoprofen, is related to the capacity to inhibit both the constitutive and inducible isoforms of cyclo-oxygenase (prostaglandin H synthase-1 and 2) and that the inhibition triggers specific bronchoconstriction which leads to a severe asthma attack (10). Szczeklik (11) reported that the capacity to inhibit cyclo-oxygenase is related to the extent of asthma attack. However in the present case, a DLST was strongly positive for ketoprofen. In addition, dibutylhydroxytoluene and rosin ester are additives which are only contained in 2.0% ketoprofen adhesive tapes and a DLST of rosin ester was weakly positive. L-menthol and oxybenzone are additives contained in 2.0% ketoprofen adhesive tapes and a DLST of rosin ester was also positive. It has been reported that many drug additives such as tartrazine, paraben, sodium benzoate and sulfate (NaHSO₃), are related to analgesic-induced asthma. We suspected that drug-induced hypersensitivity coexisted with analgesic-induced asthma, although they do not have the capacity to inhibit cyclo-oxygenase (1). The fact that only high-dose ketoprofen adhesive agents caused life-threatening asthma makes it possible to hypothesize that only products which only contain high-dose adhesive agents, dibutylhydroxytoluene or rosin ester, cause severe attacks. A DLST of the latter was weakly positive, but it has not been reported that rosin ester was related to analgesic-induced asthma. We suspected that drug-induced hypersensitivity coexisted with analgesic-induced asthma in the present case, but it is not clear whether or not the hypersensitivity was related to the pathogenesis of the asthma.

Elimination from the environment of the causative agents of analgesic-induced asthma would be the most successful means to treat this disease. Bronchodilators and glucocorticoids are also available for treatment of analgesic-induced asthma as well as for of conventional asthma. However, glucocorticoids should be used with caution in patients with analgesic-induced asthma; in some cases cross-sensitivity to steroid succinate esters has been reported (12). The present patient was extubated after 20 hours by administration of 500 mg of aminophylline and 400 mg of hydrocortisone sodium succinate because she had no cross-sensitivity of steroid succinate esters. The fact that the interval from intubation to extubation is shorter in analgesic-induced asthma than in conventional asthma may be one of the characteristics of this disease.

While it is commonly known that NSAIDs are contraindicated in patients with analgesic-induced asthma, it is not well known whether or not NSAIDs adhesive patches can cause life-threatening asthma. Even if patients with analgesic-induced asthma have been using some NSAIDs adhesive patch, other adhesive agents containing the same NSAIDs are not necessarily safe at higher doses. We suggest that NSAIDs adhesive patches were presented with caution in bronchial asthma patients and only after confirming the absence of a history of analgesic-induced asthma.

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References