

CASE REPORT

Flurbiprofen Axetil, Nasal Polyps, and Status Asthmaticus: An Unusual Case Report

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Introduction. Herein, we report a case of life-threatening status asthmaticus in a young male presented with nasal polyps but without any history of anaphylaxis or asthma. **Discussion.** The patient had normal results from preoperative respiratory systemic examinations. The postoperative asthma, which started after an infusion of nonsteroidal anti-inflammatory drugs (NSAIDs), was severe and difficult to manage. A relationship between the NSAID infusion and the asthma attack was indicated. Flurbiprofen axetil, a nonselective COX2 inhibitor, is most likely the causative agent in this case, although there are no prior reports of asthma caused by this agent. **Conclusion.** We concluded that flurbiprofen axetil evoked severe bronchospasm in this case. Patients who are sensitive to flurbiprofen axetil will usually react to other NSAIDs; therefore, other ordinary NSAIDs should be used with caution in hypersensitive patients. An intranasal ketorolac challenge in individuals with nasal polyps, which is a novel and safe alternative to aspirin challenge, may be recommended to rule out aspirin-exacerbated respiratory disease, prior to the systemic administration of NSAIDs.

Keywords aspirin-exacerbated respiratory disease, bronchospasm, endoscopic sinus surgery, flurbiprofen axetil, nasal polyps, NSAIDs, status asthmaticus

INTRODUCTION

Concomitant aspirin intolerance, intrinsic bronchial asthma, and nasal polyps are referred to as aspirin-induced asthma, also known as aspirin-exacerbated respiratory disease (AERD). To avoid life-threatening situations, anesthesiologists avoid using nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with a history suggestive of AERD. Herein, we report an emergency case of status asthmaticus after NSAID infusion for analgesia postoperatively. The patient undergoing endoscopic sinus surgery had no known allergic or asthmatic history.

CASE REPORT

A 24-year-old male with a history of “intermittently having a stuffy nose for 4 years” was scheduled for endoscopic sinus surgery under general anesthesia. He had no prior history of surgery or anesthesia, systemic complications, elicit drug use, drug allergies (especially NSAIDs), exercise intolerance, or alcohol abuse. The patient had a prior history of smoking for 6 years. The general physical examination was essentially normal, except for the change in bilateral itchi chinensis in the middle nasal canal. The sinus CT scan indicated that thickened mucosa and excreta had accumulated in the bilateral maxillary sinus, frontal sinus, ethmoidal sinus, and sphenoidal sinus. Furthermore, we observed obstruction of the bilateral nasal cavity by irregular-shaped soft

tissue (1.3×2.0 – 1.6×2.5 cm). Hypertrophy was present in right lower turbinate. Essential preoperative tests on arterial blood gases revealed a pH of 7.40, P_{O_2} 13 kPa, P_{CO_2} 5.5 kPa. The lung function exam revealed the following: forced vital capacity (FVC) of 3.59 L (89%), forced expiratory volume in 1 second ($FEV_{1.0}$) of 2.89 L (96%), FEV_1/FVC of 81%, a residual volume of 1.93 L, and maximal voluntary ventilation of 131 L/min. The bronchodilator test was negative. The routine blood test showed WBC of $13.1 \times 10^9/L$ and hematocrit of 49%. The remainder of the examination was normal.

Standard anesthesia monitoring was instituted for surgery. Blood pressure, heart rate, and oxygen saturation was recorded as 118/72 mmHg, 68 beats/min, and 98%, respectively. Induction of anesthesia and endotracheal intubation were uneventful. Bilateral breath sounds were heard during auscultation. The surgery was initiated after the patient was sufficiently anesthetized. Propofol 60–80 $\mu g/kg/min$ and remifentanyl 0.1–0.2 $\mu g/kg/min$ were continuously infused in combination with inhaled sevoflurane (1%) for the maintenance of anesthesia. Nicardipine 0.5–1.5 $\mu g/kg/min$ was used to control hypotension. During the operation, the peak inspiratory pressure was 15–16 cmH₂O and end-tidal CO₂ (P_{ETCO_2}) was 34–35 mmHg with a tidal volume of 6 mL/kg. Circulation and respiration parameters were monitored to observe anesthesia efficacy, complications, and adverse reactions intraoperatively. The surgery lasted approximately 100 min, and anesthetic management went smoothly. Flurbiprofen axetil (50 mg) and luxin (granisetron, 3 mg) were given by intravenous infusion 15 min before the end of surgery. The patient appeared restless during aspiration of sputum from the trachea. Extubation of the tube was performed after the extubation

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criteria were satisfied, and the aspirated oral secretion was clean. The patient was transported to a recovery room once fully awake, following verbal commands, breathing spontaneously, and oxygenating adequately.

Upon arrival to the recovery room, the patient presented with extreme acute agitation and 2 min later struggled to sit up. The symptoms rapidly progressed into lip cyanosis, dyspnea, and loss of consciousness. There were no signs of angioedema or skin erythema. Auscultation of the lungs (bilateral) revealed an absence of breath sounds that was not improved with 100% oxygen delivered via facemask and methylprednisolone (160 mg). The patient's blood pressure, heart rate, and SpO₂ fell to 150/90 mmHg, 165 beats/min, and 60%, respectively. The patient displayed whole body cyanosis and was unresponsive. The patient was immediately intubated after the infusion of succinylcholine (100 mg). Manual ventilation was rather difficult due to severe airway resistance. Bilateral auscultation revealed diffused wheezing sounds that were more prolonged in the expiratory phase. Due to bronchospasms that persisted 5 min after intubation, the patient was administered an additional 200 mg methylprednisolone, 100 mg lidocaine, and 100 mg ketamine. However, the additional drugs did not alleviate the diffused wheezing sound and the symptoms were not significantly alleviated. Arterial blood-gas analysis on 100% oxygen revealed pH 6.94, P_{CO2} 15.96 kPa, P_{O2} 1.33 kPa, and BE -10 mmol/L. In order to stabilize the patient, a solution containing sodium bicarbonate (250 mL) and aminophylline (0.25 g) was administered by intravenous infusion. After 10 min, reexamination of arterial blood-gas showed: pH 7.02, P_{CO2} 12.10 kPa, and P_{O2} 13.3 kPa, and the symptoms slowly improved. Mechanical ventilation was instituted at the lung-inhaled oxygen rate of 4–8 L/min, tidal volume of 9 mL/kg, and a respiratory rate of 18/min. The patient's peak inspiratory pressure rose to 43–50 cmH₂O and P_{ET}CO₂ rose to 43–45 mmHg. Blood-gas analysis revealed a pH 7.24, P_{CO2} 7.98 kPa, P_{O2} 11.97 kPa, and BE -2.7 mmol/L. The monitoring revealed a blood pressure, heart rate, and SpO₂ of 95–80/65–45 mmHg, 90–110 beats/min, and 96–97%, respectively. Urine output was 350 mL. The patient was hemodynamically stable for the remainder of the recovery period. He remained intubated and was admitted to the intensive care unit 50 min later. The patient was diagnosed with severe status asthmaticus based on the following observations: progressive respiratory failure due to asthma, failure of conventional therapeutic interventions with tracheal intubation failing to provide sufficient oxygenation, marked expiratory wheezing, markedly diminished or absent breath sounds, central cyanosis, agitated progression into coma, and respiratory failure with P_{O2} <70 mmHg in 100% O₂. Chest X-ray was normal. The selected drug treatment consisted of methylprednisolone, inhaled salbuterol, and theophylline, which may have remarkably improved his symptoms. Bronchospasms were still present after drug treatment and the patient's pulmonary function test showed: FVC

of 1.09 L, FEV_{1.0} of 0.59 L (19.6%), FEV_{1.0}/FVC of 54%, and maximal voluntary ventilation of 59 L/min. A positive tryptase (25.2 µg/L) and urine histamine (82.71 µmol/L) analysis, taken 1 hour after the attack, suggested mast cell degranulation. There was no family history of allergies upon further investigation. Pathological findings from the removed polyps indicated cell swelling and basal membrane thickening. Inflammatory cells distributed in the tissues consisted of infiltrating eosinophils and mast cells. Fifteen hours later, the patient was extubated successfully, had normal mental status, and no wheeze was present. Further physical examination indicated that the patient was physically normal. All vital signs were within normal ranges and the patient was discharged from hospital 2 days later.

DISCUSSION

In this case, we ruled out potential triggers of bronchospasm. First, the surgery was uneventful, therefore we ruled out intravenous anesthetics and anaphylaxis followed by propofol, rocuronium, sufentani, or remifentanyl, considering that anaphylactoid reactions of these drugs usually occur within minutes of exposure (1, 2). Second, since the patient's ECG and chest radiography were normal, we excluded congestive heart failure and recurrent small pulmonary emboli and pneumothorax, which can manifest with sudden respiratory dysfunction. Third, based on fiberbronchoscopy, we excluded obstruction of excretion or foreign matter. Fourth, we ruled out the stimulation of aspiration or tracheal extubation, which mainly causes upper respiratory tract obstruction rather than consistent lower respiratory tract contraction. Fifth, upper and lower respiratory tract eosinophil infiltration is a key feature of AERD. Because our patient refused further testing (such as intranasal ketorolac or oral aspirin challenge) after full explanation of the potential risks, we could not confirm our diagnosis of AERD.

Flurbiprofen axetil was most likely the causative agent in this case, although there are no prior reports of asthma caused by this agent. When flurbiprofen axetil is injected intravenously as a single dose of 5 mL to an adult patient, it is rapidly hydrolyzed into flurbiprofen and blood concentration peaks 5–10 min after administration (3). The onset of asthma, laboratory findings (analysis of serum tryptase, which is related to the progression of AERD (4) and histamine in urine), and the symptoms (e.g., tachycardia, hypotension, continuous and progressive airway inflammation, and immediate impact of central nervous system) indicated a relationship between NSAID infusion and the asthma attack. We further suggest that this was exacerbated by polyposis.

The *British National Formulary* places emphasis on the usage of cyclo-oxygenase (COX) inhibitors in asthma, and carries a specific warning that any degree of bronchospasm could be related to the NSAIDs (3). Flurbiprofen axetil belongs to the family of nonselective COX2 inhibitors. It is an intravenously administered

NSAID for postoperative analgesia and for controlling various types of cancer pain through inhibition of biosynthesis of prostaglandin. It has been reported to precipitate side-effects similar to other nonselective NSAIDs (such as gastrointestinal ulcers, impairment of function of liver and kidney, bronchospasm, granulocytopenia, etc.) (5). The pathogenesis of asthma secondary to flurbiprofen axetil is thought to be mediated by inhibition of the PGE₂ pathway, leading to an increase in the synthesis of leukotrienes. Evidence suggests that leukotrienes are effective in exerting a powerful bronchoconstriction and edema of tracheal mucous, producing severe allergen-like effects (6). Patients who are sensitive to flurbiprofen axetil will usually react to other NSAIDs; therefore, other ordinary NSAIDs should be used with caution in hypersensitive patients.

Bronchial reflection, acute/chronic nasal sinusitis, and polyps may aggravate or evoke asthma (7). The association of bronchial asthma and nasal polyposis in aspirin-intolerant patients was first described by Widal in 1922 (8) and has been confirmed by several reports (9, 10). Aspirin-induced asthma is frequently characterized as AERD, which is a clinical syndrome including nasal polyps, chronic hypertrophic eosinophilic sinusitis, asthma, and sensitivity to aspirin or other NSAIDs (mainly inhibits COX1 enzymes) (11). It occurs in middle-aged individuals (20s and 30s are the most common onset ages) and may not include any allergies. Asthmatics with nasal polyps that do not suffer typical asthmatic symptoms or adverse reactions with NSAIDs still have relatively high rate of NSAID intolerance. Persistent bronchospasm, as seen in this clinical presentation, is also consistent with "status asthmaticus" (12).

Since our patient was suffering from nasal polyposis and severe asthma, we concluded that he was probably sensitive to NSAIDs and would be classified as high risk for AERD. The first approach to treating AERD is to prevent these patients from using aspirin and other NSAIDs with similar activity. Most patients can tolerate highly selective COX2 inhibitors, and treatment is usually not associated with complications (13). After a prompt diagnosis, patients with asthma or asthmatic symptoms should be administered large doses of inhaled corticosteroids in addition to conventional therapy (such as β agonists, aminophylline, and anticholinergic drugs). An accurate diagnosis, maintenance of circulation, and keeping the respiratory tract unobstructed are keys to successfully treating acute asthmatic attacks in patients. Cardiovascular drugs (e.g., adrenalin) and reasonable volume expansion therapy should be applied when hemodynamics are unstable. Tracheostomy is often necessary when tracheal intubation is difficult. Up to 25% of hospital admissions for acute asthma status requiring mechanical ventilation may be due to NSAID ingestion (14). Furthermore, in order to prevent respiratory system

infection due to tracheal obstruction, a suitable dose of broad-spectrum antibiotics should be applied when asthmaticus is present. Finally, acidosis and electrolyte disturbances must be corrected in a timely manner to avoid tissue and organ injury.

CONCLUSION

We conclude that flurbiprofen axetil was the risk factor evoking consistent severe bronchospasm in our case. A thorough review of clinical history may prevent adverse reactions to NSAIDs, and if there is a possibility of suspected AERD, it is wise to choose a safer drug, such as highly selective COX2 inhibitor.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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