E-Da Medical Journal 1 (2014) 24-29

**Case Report**

# Suspected Cephalexin-Associated Bronchospasm during General Anesthesia Procedure: Report of a Case Series

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Bronchospasm is a life-threatening incident during anesthesia. In addition to IgE-mediated anaphylaxis, there are also a lot of conditions and drugs that can induce bronchospasm through various mechanisms, including gastric acid aspiration, irritating gas inhalation, endotracheal intubation, muscarinic receptor agonists, beta blockers, and histamine-releasing drugs. Immediate treatment with bronchodilator or epinephrine can be lifesaving. We report six cases of bronchospasm during general anesthesia, and review the possibly related mechanisms. From the clinical courses, we deduce that intravenous cephalexin, when used as prophylactic antibiotics, induces bronchospasm under general anesthesia through eliciting an adverse drug reaction instead of IgE-mediated anaphylaxis.

**Key words:** bronchospasm, anaphylaxis, cephalexin, general anesthesia

Anaphylaxis may present with severe symptoms such as bronchospasm or cardiovascular collapse. The incidence of anaphylaxis and anaphylactoid reactions under anesthesia is estimated to be between 1 in 3,500 to 1 in 13,000.[1] The agents that frequently cause anaphylactic reactions during anesthesia are neuromuscular blocking agents (69.2%), latex (12.1%), and antibiotics (8.0%), followed by hypnotics (3.7%), opioids (1.4%) and other agents.[2] Anaphylaxis can be caused by IgE-mediated reactions, non-IgE-mediated immunologic reactions as well as nonimmunologic reactions which mimic allergy (drug idiosyncrasies, drug intolerance, direct toxicity, drug interactions or overdose).[3,4] The treatment strategies include administration of bronchodilators, anti-histamines, steroids, and epinephrine.

In fact, the exact cause of anaphylaxis during anesthesia is difficult to be identified as multiple medications were administered sequentially within a very short period. Furthermore, most drug reactions were adverse rather than allergic. Bronchospasm is a sudden constriction of the muscles in the walls of the bronchioles. It causes difficult breathing which can be mild or severe. Beside anaphy-

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laxis, vagal activation, neurotransmitters, or drugs can also induce bronchospasm via biochemical changes of smooth muscle cell in the airway, leading to airway contraction.[5] For bronchospasm, bronchodilating drugs are used. In severe cases, immediate treatment with epinephrine can be lifesaving. Supportive care with mechanical ventilation may be required.

We report a case series of bronchospasm during general anesthesia. We suspect that prophylactic intravenous cephalexin induces bronchospasm during general anesthesia through an unknown adverse reaction instead of IgE-mediated anaphylaxis.

## Case Report

**Case 1**

A 31-year-old man, height 168 cm, weight 75 kg, without known systemic diseases, was admitted with the diagnosis of left thumb and index contracture for tendon transfer. Multiple anesthetics, including fentanyl 150 μg, propofol 170 mg, xylocain 60 mg, and cisatracurium 2 mg, were given sequentially. Then laryngeal mask airway (LMA) was inserted and general anesthesia was maintained with sevoflurane. About 10 minutes after induction, 1 gm of cephalexin (Roles) as prophylactic antibiotics was injected intravenously. Five minutes later, bronchospasm happened. The symptoms subsided after treatment with salbutamol and hydrocortisone. The surgery was completed without complication.

**Case 2**

A 60-year-old man, height 156 cm, weight 62 kg, with a history of hypertension and asthma for 10 years, and old stroke with seizure and right-side weakness, was diagnosed as having L3-4-5-S1 spinal stenosis for spinal fusion. Multiple anesthetics, including fentanyl 150 μg, midazolam 5 mg, propofol 130 mg, xylocain 40 mg, and rocuronium 50 mg, were given sequentially. Then endotracheal tube was inserted and general anesthesia was maintained with desflurane. About 35 minutes after induction, cephalexin 1 gm was administered intravenously. Bronchospasm occured 5 minutes later. The symptoms subsided after treatment with hydrocortisone. The surgery was completed without complication. Intriguingly, postoperatively this patient received three more doses of cephalexin injection in the ordinary ward smoothly.

**Case 3**

A 28-year-old man, weight 103 kg, with herb-taking history underwent right knee arthroscopic reconstruction. Multiple anesthetics, including fentanyl 200 μg, propofol 200 mg, xylocain 40 mg, rocuronium 40 mg, and cisatracurium 10 mg, were given sequentially. Then endotracheal tube was inserted. General anesthesia was maintained with desflurane. About 20 minutes after induction, cephalexin 1 gm was given intravenously. Severe bronchospasm happened and $SpO_2$ dropped to 88% immediately. The symptoms subsided after treatment with terbutaline, aminophylline, and hydrocortisone. The surgery was completed without complication.

**Case 4**

A 22-year-old man, weight 65.5 kg, without any known systemic disease, was admitted with the diagosis of left radial fracture for open reduction and internal fixation. Multiple anesthetics, including fentanyl 100 μg, propofol 140 mg, xylocain 60 mg, and rocuronium 20 mg, were given sequentially. LMA was inserted and general anesthesia was maintained with desflurane. About 15 minutes after induction, cephalexin 1 gm was given intravenously. Severe bronchospasm was evident 5 minutes later. The symptoms subsided after treatment with epinephrine, aminophylline, and hydrocortisone. The surgery was completed without complication.

**Case 5**

A 71-year-old man, height 174 cm, weight 58 kg with a medical history of diabetes mellitus and hypertension, was diagnosed as having L2-5 spinal stenosis for spinal fusion. Multiple anesthetics, including fentanyl 150 μg, propofol 200 mg, xylocain 60 mg, and rocuronium 50 mg, were given sequentially. Then endotracheal tube was inserted. General anesthesia was maintained with desflurane and cisatracurium. About 35 minutes after induction, the first dose of cephalexin 1 gm was given intravenously. Due to prolonged operation, a second dose of intravenous cephalexin was injected about 4.5 hours following the induction. Bronchospasm happened soon after the second dose of cephalexin. The symptoms subsided after treatment with hydrocortisone. The surgery was completed without complication.

**Case 6**

Events of the former 5 cases happened successively from Dec. 11th to 13th, 2006. Actually there were more cases of bronchospasm in our operation theater (OR) during that period. Thereafter, our pharmaceutical committee prohibited the use of cephalexin during operation. Since other prophylactic antibiotics were used, no such incident happened again, until 2 years later on Jul. 9th, 2008, when cephalexin was accidentally brought to the OR with the patient (case 6), resulting in bronchospasm as described below:

A 40-year-old man, weight 117 kg, with hypertention and multiple drugs allergy history, underwent arthroscopy for evaluation of osteoarthritis of his right knee. Multiple anesthetics, including fentanyl 150 μg, citosol 500 mg, succinylcholine 100 mg, and cisatracurium 6 mg, were given sequentially. Then endotracheal tube was inserted. General anesthesia was maintained with desflurane. About 25 minutes after induction, cephalexin 1 gm was injected intravenously. Severe bronchospasm and bradycardia developed 5 minutes later. The symptoms subsided after treatment with epinephrine and hydrocortisone. The operation was cancelled. Interestingly, we traced this patient's previous record and found that he had received arthroscopy for assessment of right traumatic osteoarthritic knee under spinal anesthesia on Nov. 12th, 2006. Cephalexin 1 gm had been injected intravenously once during the procedure. However, it was uneventful at that time.

*Table 5. Summary of demographic characteristics, underlying illness, airway instrumentation, and anesthetics use in the six bronchospasm cases.*

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Age (y/o) | 31 | 60 | 28 | 22 | 71 | 40 |
| Gender | male | male | male | male | male | male |
| Underlying illness | | | | | | |
| asthma | | + | | | | |
| drug allergy history | | | | | | + |
| hypertension | | + | | | + | + |
| diabetes mellitus | | | | | + | |
| cerebrovascular attack | | + | | | | |
| Airway instrumentation | | | | | | |
| endotracheal tube | | + | + | | + | + |
| laryngeal mask | + | | | + | | |
| Anesthetics | | | | | | |
| Thiamylal | | | | | | + |
| propofol | + | + | + | + | + | |
| cisatracurium | + | | + | | + | + |
| rocuronium | | + | + | + | + | |
| anectine | | | | | | + |
| desflurane | | + | + | + | + | + |
| sevoflurane | + | | | | | |
| Special events | | a | | | b | c |

a: This patient received three more doses of intravenous cephalexin in the ordinary ward uneventfully.
b: The event happened after the second dose injection, instead of the first dose.
c: Cephalexin had been injected once during an operation under spinal anesthesia 2 years ago uneventfully.

## Discussion

In 2006, intravenous cephalexin (Roles) was used as pre-operative prophylactic antibiotics at our institute, until the events of bronchospasm caught our attention. Although our suspicion of cephalexin being the causative agent was first declined by the surgeons who regarded it as a routine antibiotic safely used

in postoperative patients, we still reported to the hospital authority that it is a likely cause of the attacks. Consequently our hospital made a compromise that this drug should be prohibited in the operation room, but allowed to be used in the ordinary ward. As a result, cephalexin was suspended in the operation room for 2 years during which no similar event occurred until two years later, in 2008, when cephalexin was taken along with one patient into the operation room incautiously, resulting in severe bronchospasm (Case 6). Subsequently, we considered anesthetic agents, endotracheal intubation, allergic history, and surgical procedures to be unlikely causes of these events, and regarded cephalexin as a risk factor. Interestingly, the attacks invariably occurred under general anesthesia.

It was reported that anaphylactic reactions to cephalosporin are rare with an incidence between 0.0001 and 0.1%.[6] Another study on 9388 patients without history of penicillin allergy who were treated with cephaloridine, cephalothin, or cephalexin showed that only 2 subjects (0.02%) developed anaphylaxis.[6,7] In fact, there were more than six events at our hospital, excluding other cases of increased airway pressure and mild bronchospasm. The incidence of bronchospasm, probably caused by cephalexin injection, is roughly estimated to be about 5-10% at our hospital. The events were likely to be adverse drug reactions rather than allergies. However, there is no study directly proving the cause-and-effect relationship between cephalexin and bronchospasm.

There is no literature available regarding the link between cephalexin and bronchospasm in the PubMed database. Wikipedia described cephalexin as an oral antibiotic different from our intravenous form (Roles).

According to the Handbook of Common Drugs, 2004 edition, all cephalexin products are in oral forms, except for cephalexin sodium (Roles) which is the only one available in intravenous form produced by a domestic pharmaceutical factory in Taiwan. The side-effects of the intravenous form mentioned in the literature are mainly gastrointestinal disorders. Furthermore, since oral drugs including this one are seldom used as prophylactic antibiotics in surgery, it would not be co-administered with general anesthetics. This may explain the lack of literature reporting the relationship between cephalexin and bronchospasm in PubMed or other medical databases.

In case 2, bronchospasm attack occurred during general anesthesia, but the patient successively received 3 doses of cephalexin in the post-operative period in the ordinary ward smoothly. It seems that the event was not IgE-mediated anaphylaxis. Instead, other factors may work with cephalexin under general anesthesia.

In case 6, years before the attack during general anesthesia, the patient had received a dose of pre-operative prophylactic cephalexin under spinal anesthesia. No discomfort was noted at that time. It seems that the event might be related to general anesthesia. Whether the episode was due to unknown interactions between cephalexin and specific anesthetic agents remains to be elucidated.

In case 5, while the first dose of intravenous cephalexin was given uneventually, the second dose administered 4.5 hours later seemed to trigger treacherous bronchospasm. This adverse reaction seems non-specific, non-allergic, and dose-dependent. Since hours passed, the effects of the induction agents had decayed, only desflurane and cisatracurium were continuously administered during that period.

Although cephalexin may play a major role, some factors related to general anesthesia may also contribute to such events. We cannot explain the high incidence of bronchospasm which was beyond the incidence by chance and also the fact that the events exclusively happened during general anesthesia.

Patients with constitution of asthma carry

a higher risk of bronchospasm during induction when they receive general anesthesia and tracheal intubation. In our six patients, who all underwent general anesthesia, one had asthma, one had drug allergic history, four received endotracheal intubation, and two were on laryngeal mask. Regardless of asthma/allergy history or tracheal intubation, immediately patients developed bronchospasm after cephalexin administration.

Volatile anesthetics, such as halothane, enflurane, isoflurane, sevoflurane, and desflurane, are potent bronchodilators that work through altering the intracellular concentration of free $Ca^{2+}$ of airway smooth muscle.[5] On the other hand, isoflurane and desflurane are very pungent and might induce an asthmatic attack through facilitating neurally mediated acetylcholine release during anesthetic induction.[8] Five of our six patients inhaled desflurane and one inhaled sevoflurane. In theory, sevoflurane is a bronchodilator without pungent odor and should act against bronchospasm. Yet bronchospasm still happened as in Case 1. Nevertheless, the episodes occurred more frequently with desflurane than with sevoflurane, in our series.

The incidence of pseudo-allergic reaction with histamine release during anesthesia is high, about 1 out of 10.[9] It could even be increased by synergism of two different kinds of drugs via non-allergic reactions. For example, vancomycin synergized with narcotics in inducing red man syndrome (flushing, pruritus, and occasionally hypotension and chest discomfort).[10] Besides, the combination of vancomycin and muscle relaxant or opioid may increase the risk of anaphylactoid reaction by enhancing histamine release in rats.[11] These adverse events were probably not true hypersensitivity mediated by IgE-dependent mechanism. Instead, they may be attributed to direct mast cell degranulation to release histamine. Vancomycin, morphine, demeral, and atracurium may potentiate histamine release that usually presented as cutaneous signs. However, the drugs used in our patients, including cephalexin, fentanyl, rocuronium, and cisatracurim seem unlikely to follow these mechanisms.

Some neuromuscular blocking drugs are capable of inducing histamine release from mast cells, and/or binding to muscarinic receptors at ganglia, nerve endings, and smooth muscle of airway to alter airway caliber. However, in contrary, rocuronium and cisatracurium are devoid of significant airway effects,[12] and either rocuronium or cisatracurium was used in our six patients during operation. Anaphylactic reactions to opioids are rare. Fentanyl does not cause nonimmunological histamine release.[13] Although both thiopental and thiamylal induce dose-related histamine release, thiamylal is significantly more potent than thiopental[14] and thiopental in turn is more potent than propofol.[15] Propofol can induce inhibition of neurally mediated acetylcholine release,[16] so that it seems to be a better choice than barbiturates in asthmatic patients. All of our six patients received fentanyl, including five received propofol and one received thiamylal. However, according to our observation in Case 5, when the event happened, the induction agents had decayed and the hypnotics may not be involved in the event.

Overall, the bronchospasm is not related to asthma, drug allergic history, endotracheal intubation, and pungent desflurane. Besides, the incidence of IgE-mediated anaphylaxis resulting from cephalexin or anesthetic agents is rare. Moreover, the possibility of nonspecific histamine release by the anesthetics in our patients is low. Furthermore, volatile anesthetics are bronchodilators and the effects of neuromuscular blockades, hypnotics, and opioids on airway smooth muscle tone are minimal. No common anesthetics were used in these 6 cases except fentanyl. From the clinical course, it is rational to suspect that cephalexin may be a major contributor to bronchospasm when its use is associated with general

anesthesia.

In conclusion, we consider intravenous cephalexin, when used as prophylactic antibiotics, to be a likely culprit causing bronchospasm under general anesthesia. Moreover, after analyzing the clinical courses of our cases, we propose that the events were more likely adverse drug reaction rather than IgE-mediated anaphylaxis or allergic reactions. However, further studies with a larger sample size are needed to disclose the truth behind the events.

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