Prophylactic Antibiotic Administration Induced Bronchospasm as Increased Airway Pressure During General Anesthesia

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Background: Anaphylactic reaction induced bronchospasm as wheezing and severe elevation of airway pressure was observed in a succession of patients during general anesthesia at our institute in November 2007. The aim of this survey was to investigate the suspected causes and risk factors of these anaphylactic reactions and the degree of correlation.

Methods: All patients who received general anesthesia between November 1 and November 10, 2007 were enrolled. Underlying diseases, substances including intravenous and inhalational anesthetics, antibiotics, and the degree of increase in airway pressure were recorded. Enrolled patients were divided into a significant-airway-pressure-elevation group (Group P) and a no-airway-pressure-elevation group (Group N).

Results: A new brand of cephalexin (Roles®) used as a prophylactic antibiotic was identified as the most likely causative substance of this succession of suspected anaphylactic reactions (28 in 185 patients, 15.14%), and rapid administration was a contributor to these anaphylactic reactions.

Conclusion: In this study, we found that rapid administration of Roles® was the main cause of suspected anaphylactic reaction presenting as bronchospasm with severe elevated airway pressure. Using Roles® as the prophylactic antibiotic is not recommended in patients receiving general anesthesia. [*J Chin Med Assoc* 2010;73(2):72–77]

Key Words: airway pressure, anaphylactic reaction, antibiotic, bronchospasm, cephalosporin, patient safety

Introduction

Anaphylactic reactions during anesthesia are rare but may have dramatic and unpredictable consequences; it may present with severe symptoms such as cardiovascular collapse or bronchospasm.[1,2] The incidence of anaphylaxis during anesthesia is very difficult to estimate.[3] The leading causes are neuromuscular blocking agents, latex, and antibiotics, followed by other induction medications. Bronchospasm in association with anesthesia may appear as an entity in its own right or may be a component of another problem such as anaphylaxis.[4,5] The key element of the management of anaphylactic reactions in the operation room is a collaborative effort between anesthesiologists and surgeons.

In November 2007, successive cases of bronchospasm manifesting as sudden and dramatic increase in inflation airway pressure and episode of diffuse wheeze without other anaphylactic symptoms such as urticaria, angioedema or hemodynamic instability occurred during general anesthesia in our institute. Some cases presented as severe bronchospasm, with difficulty in ventilation and very high airway resistance. All of the cases were effectively treated by intravenous steroids and lidocaine, inhaled or intravenous bronchodilator, and even intravenous epinephrine. It is of the utmost importance to clarify the cause of the successive suspected anaphylaxis cases or the interaction between causative substances. This is also important since patients and anesthesiologists need to be informed about exposure to the identified substance(s) and risk factors.

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Therefore, we report herein the investigation and crisis management of this succession of cases of anaphylaxis induced by a prophylactic antibiotic.

The goal of this study was to determine the causes of the suspected anaphylactic reactions and to stop further episodes. We investigated all the cases by reviewing the anesthesia records. The preliminary data revealed that a prophylactic antibiotic, cephalexin (Roles®; Gentle Pharmaceutical Corporation Kashin Medicines Co., Ltd., Yunlin, Taiwan), which had been administered in most cases as a prophylactic antibiotic after the induction of general anesthesia, may have played an important role. Anaphylaxis induced by this medication was highly suspected, and perioperative use of this antibiotic was reduced after our announcement of the possibility of it causing bronchospasm during general anesthesia.

Methods

This retrospective study was conducted at Taipei Veterans General Hospital and was approved by the hospital's institutional review board. We carried out a retrospective survey by reviewing the medical and anesthesia records of all patients of ASA Class 1 to 3 who received general anesthesia at our hospital between November 1 and November 10, 2007. Demographic data and information regarding underlying diseases were collected for each patient, and all substances to which each patient had been exposed, including intravenous and inhalational anesthetic agents for general anesthesia and prophylactic antibiotics, were recorded. The interval between endotracheal intubation and antibiotic administration, and the duration of antibiotic administration were also obtained from the anesthesia records. The tidal volume was set at 7–10 mL/kg on the time-cycled ventilator of the anesthesia machine. Airway pressure after endotracheal intubation and sequential changes after the administration of prophylactic antibiotics were collected every 5 minutes during the whole course of general anesthesia. The prophylactic antibiotic was selected by the surgeon in each case, and the diagnosis and management of bronchospasm (elevated airway pressure and auscultated wheezing) were determined by each patient's independent attending anesthesiologist.

Details were obtained regarding the degree of elevation of airway pressure as compared with after intubation. In order to identify the severity of bronchospasm in this study, we divided patients into several groups by the degree of elevation of inspiratory pressure. The severity of elevation was graded from 0 to 5, indicating least to greatest severity [grade 0 = airway pressure elevation of 0–2 cmH_2O; grade 1 = elevation of 3–5 cmH_2O; grade 2 = elevation of 6–10 cmH_2O; grade 3 = elevation of 11–15 cmH_2O; grade 4 = elevation of 16–20 cmH_2O; grade 5 = elevation $\geq$ 21 cmH_2O (defined as severe bronchospasm)]. A significant elevation of airway pressure was defined as grade 1 or above; resolution of the reaction was defined as the airway pressure decreasing back to grade 0.

Statistical analysis

All statistical analyses were carried out using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows. Patients were divided into a significant-airway-pressure-elevation group (Group P) and a no-airway-pressure-elevation group (Group N) according to whether or not there was elevation of airway pressure after the administration of prophylactic antibiotics. Continuous data are presented as mean ± standard deviation, and categorical data as counts with percentages.

The independent *t* test or χ^2 test was used to compare patients' characteristics, patients' medical history, and variables related to the airway pressure of the 2 groups as appropriate. A p value < 0.05 was considered to indicate statistical significance. In univariate analysis, the odds ratio (OR) of each variance was estimated using logistic regression analyses with enter mode. Forward stepwise logistic regression was performed with preassigned p values equal to 0.05 for the further multivariate analysis. The OR of each variable was also expressed with a 95% confidence interval (CI).

Results

In total, 185 patients who underwent general anesthesia in this period were investigated, 30 of whom developed significant elevation of airway pressure (Group P). All episodes of elevated airway pressure or bronchospasm subsided after treatment, and all surgery was completed without sequelae. The groups were compared with respect to age, weight, height, underlying systemic diseases, and previous allergic history. The intravenous and inhalational anesthetic agents administered, and the interval between intubation and antibiotic administration were also compared, and did not differ significantly between groups (Table 1).

After the administration of cephalexin, specifically Roles®, as a prophylactic antibiotic, 28 patients developed significant elevation of airway pressure (28 *vs.* 43, $p < 0.05$), whereas with cefazolin (Cefa®; Taiwan Biotech Co., Ltd., Taoyuan, Taiwan), only 2 patients developed a reaction (2 *vs.* 68, $p < 0.05$). The degree of airway pressure elevation in both of the patients

Table 1. Demographic and anesthesia data of the enrolled patients*

	Group P ($N=30$)	Group N ($N=155$)	p	Total ($N=185$)
Sex (male)	14 (47)	89 (57)	0.278	103 (55.68)
Age (yr)	56.30 ± 20.52	52.53 ± 19.48	0.337	53.14 ± 19.65
Body weight (kg)	61.45 ± 12.79	63.83 ± 15.42	0.428	63.44 ± 15.02
Body height (cm)	158.25 ± 10.02	161.70 ± 13.02	0.171	161.14 ± 12.62
BMI (kg/m^2)	24.31 ± 3.35	24.15 ± 4.40	0.850	24.17 ± 4.24
Hypertension	13 (43)	49 (32)	0.213	62 (33.51)
Diabetes mellitus	8 (27)	21 (14)	0.181	29 (15.68)
CAD	2 (7)	6 (4)	0.719	8 (4.32)
COPD	0 (0)	2 (1)	0.532	2 (1.08)
Asthma	2 (7)	3 (2)	0.144	5 (2.70)
Allergic history	1 (3)	5 (3)	0.976	6 (3.24)
Isoflurane	12 (40)	70 (45)	0.602	82 (44.32)
Desflurane	11 (37)	44 (28)	0.364	55 (29.73)
Sevoflurane	7 (23)	40 (26)	0.776	47 (25.41)
Roles®	28 (93.33)	43 (27.74)	0.000†	69 (37.30)
Cefa®	2 (6.66)	68 (43.87)	0.000†	70 (37.84)
Interval (min)	35.27 ± 20.45	28.89 ± 27.39	0.228	29.92 ± 26.44
Duration (min)	19.00 ± 7.00	31.07 ± 15.27	0.000†	29.11 ± 14.93

**Data presented as n (%) or mean ± standard deviation; †$p < 0.05$. BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; Interval = interval between intubation and antibiotic administration; Duration = duration of antibiotic administration.*

who were administered Cefa® was grade 2, which was less severe than the degree of elevation in the patients administered Roles®, which ranged from grade 2 to grade 5 (Table 2). The mean duration of antibiotic administration was 19.00 ± 6.99 minutes in Group P, compared with 31.07 ± 15.27 minutes in Group N ($p < 0.05$). No differences were observed between the 2 groups when histories of allergy, asthma, or chronic obstructive pulmonary disease were compared (Table 1).

The crude and adjusted ORs of some potential risk factors related to airway pressure elevation are displayed in Table 3. In the univariate analyses, we found that administration of Roles® was associated with significant airway pressure elevation, and that Roles® was the most significant factor related to airway pressure elevation (crude OR, 16.930; 95% CI, 5.580–51.364). In contrast, the duration of antibiotic administration played a protective role against airway pressure elevation (crude OR, 0.905; 95% CI, 0.855–0.958). Other factors did not have a statistically significant influence on airway pressure elevation. After logistic regression using a forward stepwise model, Roles® was still found to be the most significant risk factor related to airway pressure elevation. The adjusted OR and 95% CI for Roles® were 21.613 and 6.728–69.430, respectively. After adjustment of all the other risk factors, only duration of antibiotic administration was included (OR, 0.899; 95% CI, 0.848–0.953).

Table 2. Airway pressure elevation grades of Group P

Grade	Roles® ($N=28$)	Cefa® ($N=2$)
2	16	2
3	5	0
4	3	0
5	4	0

Discussion

Bronchospasm is an abnormal contraction of the smooth muscle of the bronchi (bronchoconstriction), resulting in an acute narrowing and obstruction of the respiratory airway. It may present with increasing airway pressure, expiratory wheeze, prolonged exhalation, or, in severe cases, complete silence on auscultation, and may be associated with other life-threatening conditions.[5–7] During the course of anesthesia, severe bronchospasm may develop in patients with obstructive airway diseases (such as asthma and chronic bronchitis) and as a result of airway manipulation, irritation of the tracheobronchial tree, or a host of other factors that provoke histamine release.[6] Often, the first manifestation of acute bronchospasm is a sudden rise in peak inspiratory pressure. Meanwhile, wheezing may be obvious on auscultation. However, difficulty in ventilation, "silent chest" or lack of wheeze is an ominous sign indicating extreme bronchospasm.[7]

Table 3. Univariate and multiple logistic regression of potential risk factors related to airway pressure elevation

	Univariate logistic regression crude OR	95% CI		Multiple logistic regression adjusted OR	95% CI	
Sex (male)	0.649	0.296	1.422			
Age	1.010	0.989	1.031			
Body weight	0.989	0.964	1.016			
Body height	0.982	0.956	1.099			
BMI	1.015	0.931	1.107			
Hypertension	1.654	0.745	3.673			
Diabetes mellitus	2.303	0.908	5.842			
CAD	1.762	0.338	9.179			
COPD	0.000	0.000	0.000			
Asthma	3.619	0.578	22.652			
Allergy history	1.034	0.117	9.184			
Desflurane	1.461	0.643	3.318			
Isoflurane	0.810	0.365	1.794			
Sevoflurane	0.875	0.349	2.194			
Roles®	16.930	5.580	51.364	21.613*	6.728	69.430
Cefa®	0.091	0.021	0.397			
Interval	1.007	0.995	1.020			
Duration	0.905	0.855	0.958	0.899*	0.848	0.953

*$p < 0.05$. *OR = odds ratio; CI = confidence interval; BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; Interval = interval between intubation and antibiotic administration; Duration = duration of antibiotic administration.*

Causes of bronchospasm include mechanical-related factors (kinking, endobronchial intubation, sputum, secretion), patient-related factors (obesity, allergic reaction, pulmonary edema, pneumothorax, aspiration of gastric contents) and surgery-related factors (position change, pneumoperitoneum) during the induction, maintenance or emergence phase of anesthesia.[6–8] A structured approach to its diagnosis and management could lead to earlier recognition and management.[9] In this investigation, all cases of perioperative bronchospasm occurred during the maintenance phase of anesthesia. Thus, possible causes during the induction phase (such as stimulus from tracheal intubation, hypersensitivity from induction agents) could be ruled out. Other mechanical-related factors and surgery-related factors were ruled out by physical examination and inspection of the endotracheal tubes. Most importantly, the bronchospasms developed after the administration of prophylactic antibiotics. During the interval between antibiotic administration and episodes of bronchospasm, no other medications were administered to these patients. In other words, the prophylactic antibiotics were the only variables during this period.

A succession of bronchospasm cases in which increasing airway pressure and expiratory wheeze occurred during anesthesia came to our attention. In these cases, the causes of bronchospasm during the maintenance phase other than anaphylaxis were ruled out by the anesthesiologists present. As already noted, it was peculiar to observe a series of bronchospasm cases within only a few weeks. We therefore hypothesized that a major causative substance or other cofactors might be involved. First, we conducted a brief survey by reviewing the anesthesia records and questioning surgeons to examine the possibility of any new medications or procedures that were introduced, and found that a new prophylactic antibiotic had indeed been administered in most of the cases in which bronchospasm developed, according to the preliminary data. The second step was to avoid the use of this antibiotic by discussion with the surgeons who had prescribed this prophylactic antibiotic during that period immediately after our brief investigation had been conducted. However, multiple medications are administered sequentially over a short period of time during general anesthesia, making analysis of the relationship between drug administration and clinical reactions difficult. We hypothesized that this specific prophylactic antibiotic was the most likely causative substance which, along with some contributive factors, induced an anaphylactic reaction. A comprehensive investigation was performed in order to ensure patient safety and discern the causative substance and any contributive factors. We also advocate the collection and analysis of data and discussion with surgeons as important responses to such a series of uncommon events.

Differentiating an allergic reaction from other symptoms occurring during anesthesia is difficult, as almost all symptoms of allergic reactions are also common side-effects of anesthesia. The fact that patients are covered with multiple surgical drapes, unconscious, and unable to speak also makes correct and fast differential diagnosis during general anesthesia difficult. In this retrospective investigation, we found that airway and respiratory manifestations of perioperative anaphylaxis, including wheezing and increased airway pressure, and even severe bronchospasm, without obvious cutaneous manifestations were sole features of Group P patients. Symptoms of allergic reaction during anesthesia, including cutaneous manifestations (erythema, angioedema, urticaria), hypotension, collapse, cardiac arrest, arrhythmia, and bronchospasm have been reported with varying incidence.[2,8,10–15] Cutaneous manifestations are more common in episodes that are not related to anesthesia;[8] therefore, during general anesthesia, early cutaneous signs of anaphylaxis often go unrecognized, meaning that bronchospasm and cardiovascular collapse are frequently the first recognized signs of perioperative anaphylaxis.[1,2,11–16]

We found that 28 of the 30 patients who developed significant elevation in airway pressure were administered Roles® as their perioperative prophylactic antibiotic. In the univariate analysis, the use of Roles® was found to be associated with significant airway pressure elevation (Table 2). As a first-generation cephalosporin, cephalexin is 1 of the most commonly-used perioperative antibiotics. Roles® is 1 brand of cephalexin, the use of which in our operating room began in November 2007. Several other brands of cephalosporin and cephalexin were also being used in our hospital, and prior to the use of this new brand of cephalexin, we had experienced sporadic incidents of anaphylactic reaction induced by antibiotics, such as skin rash and cardiovascular collapse. But of note, it was curious that the suspected successive anaphylactic reactions occurred after the use of Roles® was introduced.

The incidence of perioperative anaphylaxis in patients under general anesthesia ranges from 1:5,000 to 1:25,000, with a mortality rate of 3.4% caused by dramatic and unpredictable consequences.[8,10,11,12] Perioperative anaphylaxis may be caused by a variety of agents with varying incidences, including muscle relaxants, latex, antibiotics, opioids, intravenous anesthetics, inhaled anesthetics, or local anesthetics.[8,11,13–19] Antibiotics were implicated in 15.1% of perioperative anaphylaxis cases in a 2-year survey conducted in France.[15] The reported frequencies vary considerably among antibiotics. Of frequently-used antibiotics, sulfonamides have been reported to most frequently cause bronchospasm, and beta-lactams have also been implicated (27% *vs.* 15%).[20] In general, cephalosporin anaphylaxis is rare, with a frequency of 0.0001–0.1%.[21–23] There have been a few case reports of anaphylactic reactions caused by penicillin and cefazolin.[21–23] However, reports of anaphylactic reactions to intravenous cephalexin administration are rare.

Prophylactic antibiotics are administered to most patients undergoing surgery under both regional and general anesthesia. Patients who had received regional anesthesia were excluded from this retrospective study because we did not observe any elevated airway pressure and the patients, who were conscious, did not complain of cutaneous or respiratory symptoms (such as cough and chest tightness). At first, we hypothesized that airway irritation or histamine-releasing medications administered during general anesthesia, including intravenous and inhalational anesthetics, were related to or contributed to the occurrence of this series of allergic reactions. Anaphylactic reactions occurring within minutes of induction are likely due to intravenous agents.[14] Furthermore, bronchospasm can develop after endotracheal intubation in patients who have a history of allergy, asthma, reactive airway disease or cigarette smoking.[6,7] Underlying diseases, especially pulmonary diseases, are also risk factors. The risk of an allergic reaction to cephalosporins in patients with a history of penicillin allergy may be up to 8 times greater than the risk in those with no history of penicillin allergy.[21,24] No differences were observed between the groups when the histories of allergy, asthma, and chronic obstructive pulmonary disease were compared in our study, and no allergic reactions to penicillin were documented or reported. In other words, we failed to find any contributing factors in those who developed an anaphylactic reaction to Roles®. This may be due to the number of cases being not large enough as, under the principles of patient safety, we halted the administration of the suspected causative allergen after our brief investigation.

We also found that the mean duration of antibiotic administration was shorter in Group P (19 minutes) than in Group N (31.07 minutes). Comparing the 2 groups, it seems that the duration of administration played a protective role against bronchospasm. Rapid intravenous administration of some antibiotics is related to anaphylactic reaction, such as red man syndrome due to vancomycin. The prophylactic antibiotic used in our patients was infused within the recommended administration time as listed in the manufacturer's instructions (5–10 minutes).

The finding that rapid administration of Roles® was the most significant factor related to bronchospasm has been communicated to the manufacturer. The clinical response to our finding included halting the use of any formulation of cephalexin or advocating slow administration of Roles®. We responded to the results of this investigation by switching back to other brands of cephalexin or cephalosporin that had not previously caused severe bronchospasm to administer to patients undergoing general anesthesia.

It has been reported that drug formulation agents (excipients) are involved in 9% of cases of perioperative anaphylaxis.[20] The mechanism of anaphylactic reaction induced by Roles® is currently unknown. Drug excipients and preservatives might be responsible for the allergic reactions, and other contributing factors may also be involved. Further study should be conducted in an animal model to clarify the causes and contributing factors.

In conclusion, rapid administration of Roles® was highly likely to be the cause of perioperative anaphylactic reaction presenting as bronchospasm with severe elevated airway pressure in this study. Using Roles® as the prophylactic antibiotic is not recommended in patients undergoing general anesthesia. The clinical responses to the cluster of anaphylactic reactions were also presented. Further testing is required to identify the mechanism of Roles®-induced bronchospasm during general anesthesia.

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