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Wheezing during Induction of General Anesthesia in Patients with and without Asthma

A Randomized, Blinded Trial

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Background: **Patients with asthma who require general anesthesia and tracheal intubation are at increased risk for the development of bronchospasm during induction. The incidence of wheezing during induction with different intravenously administered agents is unknown. A randomized, double-blinded prospective study was undertaken to evaluate the incidence of wheezing in asymptomatic asthmatic and nonasthmatic patients receiving three commonly used intravenous anesthetic agents for induction of anesthesia.**

Methods: **Fifty-nine asymptomatic asthmatic and 96 nonasthmatic patients of ASA physical status 1 and 2 were studied. All patients received 1.5 μg/kg fentanyl, oxygen, followed by either 5 mg/kg thiopental or thiamylal, 1.75 mg/kg methohexital or 2.5 mg/kg propofol, 1.5 mg/kg succinylcholine, tracheal intubation, and inhalational anesthesia. Wheezing was assessed by an independent blinded observer auscultating the lungs at 2 and 5 min postintubation. Data were analyzed by Pearson's chi-squared, Fisher's exact test, and multiple logistic regression with significance set at $P < 0.05$.**

Results: **Both asthmatic and nonasthmatic patients who received a thiobarbiturate for induction had a greater incidence of wheezing than did patients receiving propofol. In asthmatic patients, 45% (23, 67) (mean and 95% confidence interval) who received a thiobarbiturate, 26% (8, 44) who received an oxybarbiturate, and none (0, 17) who received propofol wheezed after intubation. In nonasthmatic patients, 16% (3, 28) who received thiobarbiturate and 3% (0, 9) who received propofol wheezed.**

Conclusions: **This study suggests that propofol should be considered for induction of anesthesia in patients, particularly those with asthma, who require timely intubation. (Key words: Anesthetics, intravenous: methohexital; propofol; thiamylal; thiopental. Asthma: bronchospasm; wheezing.)**

PATIENTS with asthma who require general anesthesia and tracheal intubation are considered to be at increased risk for the development of bronchospasm during anesthesia. Factors thought to minimize this risk are the avoidance of endotracheal tubes[1] and the use of inhalational anesthetics.[2–5] It is not always possible to avoid the use of endotracheal tubes or to anesthetize the patient with inhalational anesthetics before intubating the trachea. Thus, induction of anesthesia with intravenous agents, followed by rapid tracheal intubation, is sometimes necessary in patients with asthma.

The incidence of wheezing, the predisposing factors during induction of anesthesia with intravenously administered anesthetics, and the outcomes in patients with asthma requiring tracheal intubation are poorly understood. Moreover, the incidence of wheezing after induction of anesthesia and intubation with different intravenously administered anesthetics in patients with well defined asthma is unknown. We therefore undertook a prospective randomized, double-blinded study to evaluate and compare the incidence of wheezing during induction of anesthesia in asymptomatic asthmatic and nonasthmatic patients requiring general anesthesia and tracheal intubation.

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Methods

Subjects and Randomization Procedure

The protocol was approved by the Committee on Clinical Investigation at the Johns Hopkins University and Hadassah University Hospitals, and written informed consent was obtained from all patients. Fifty-nine patients (9 men and 50 women, between the ages of 18 and 75 yr, mean age 38.6 ± 1.2 yr) with a history of active or inactive asthma, scheduled for elective surgery, and requiring general anesthesia and an endotracheal tube were enrolled in the study. Patients were defined as having active asthma[6] if they presented with a history of recurrent attacks of wheezing provoked by exogenous factors such as allergens, irritants, exercise, or viral infections and/or were taking chronic medications for their disease within the 2 yr before the scheduled surgery. Patients were defined as having inactive asthma if they presented with a history of recurrent attacks of wheezing provoked by exogenous factors in the past but not in the 2 yr before this scheduled surgery and had taken no medication for wheezing within the past 2 yr. Patients were excluded from the study if they were actively wheezing preoperatively or if their ASA physical status was 3 or higher. We enrolled 29 asthmatic patients at Johns Hopkins and 30 asthmatic patients at Hadassah. Patients were randomly assigned to one of three anesthetic induction agents: 5 mg/kg of thiamylal/thiopental (n = 20), 1.75 mg/kg methohexital (n = 23), or 2.5 mg/kg propofol (n = 16). Randomization was carried out using a random-number table.

Ninety-six healthy nonasthmatic patients (18 men and 78 women, between the ages of 18 and 75 yr, mean age 36.0 ± 1 yr) scheduled for elective surgery and requiring general anesthesia and tracheal intubation were separately and concurrently enrolled to assess the underlying incidence of wheezing in the surgical population. Nonasthmatic patients were excluded from the study if their ASA physical status was 3 or higher or if they presented with a history of any pulmonary disease. We enrolled 37 nonasthmatic patients at Johns Hopkins and 59 nonasthmatic patients at Hadassah. The nonasthmatic patients were randomly assigned to one of the three anesthetic induction agents outlined above (n = 32 for each group).

The initial sample size for asthmatic patients was based on a reported incidence of wheezing with thiobarbiturates of 6%.[1] Calculations were based on a type I error of 0.05 and a type II error of 0.20 (power of 80%). Because the incidence of wheezing with thiobarbiturates was much greater than expected, the study was stopped early with a smaller sample size.

Anesthetic Protocol

After applying standard monitoring devices (electrocardiogram, pulse oximeter, and noninvasive blood pressure monitor), all study patients received 1.5 μg/kg fentanyl followed by preoxygenation. Anesthesia was induced with 5 mg/kg thiamylal/thiopental, 1.75 mg/kg methohexital, or 2.5 mg/kg propofol intravenously over 30 s. These doses were chosen because they represented the recommended upper limits of the dose range for each drug needed to induce anesthesia. Thiamylal was used at the Johns Hopkins because it was the only thiobarbiturate induction agent on the hospital formulary. Thiopental was used at Hadassah for the same reason. Subsequently, 1.5 mg/kg succinylcholine was given intravenously, and the trachea was intubated after 60 s of manual ventilation by mask with 100% O_2. Immediately after intubation, isoflurane, approximately 2% in 60% N_2O with the balance oxygen, was administered at a rate of 6 l/min of total flow. Wheezing was assessed by an independent blinded observer at 2 and 5 min postintubation. Wheezing after 5 min was subsequently treated by the administration of a β_2-selective bronchodilator aerosol.

Data Collection

The presence of wheezing was determined through auscultation during controlled ventilation with a tidal volume of 10 ml/kg. A simple "yes" or "no" was obtained, and no grading was done. Hemoglobin oxygen saturation, end-tidal carbon dioxide, airway pressure, and systemic blood pressure were recorded. Data were obtained before induction of anesthesia, where possible, and 2 and 5 min after intubation. Wheezing was defined as high-pitched expiratory rhonchi[7] at 2 or 5 min postintubation. Data also were collected on the use of medications and cigarettes.

Statistical Analysis

For the primary analysis, the effect of induction agent on the incidence of wheezing was stratified by the presence or absence of asthma. The common relative risk was estimated by taking a weighted average of the stratum-specific relative risks. To minimize the overall variance, we selected weights proportional to the inverse of the variance of each relative risk, and to obtain *P* values and confidence intervals, exact tests[8] for strat-

Table 1. Demographic Data

	Thiobarbiturate	Oxybarbiturate	Propofol
Asthmatic group			
No. of subjects	20	23	16
Male/female	4/16	2/21	3/13
Age (yr) (mean ± SD)	39.6 ± 13.0	37.9 ± 13.4	38.6 ± 11.2
Active asthma/inactive asthma	18/2	21/2	15/1
No. of smokers	4	9	2
No. of subjects receiving medications	10	10	7
Nonasthmatic group			
No. of subjects	32	32	32
Male/female	2/30	11/21	5/27
Age (yr) (mean ± SD)	37.8 ± 10.7	36.4 ± 10.2	33.8 ± 9.6
No. of smokers	14	11	13

ified contingency tables were used. Because those tests are based on the odds ratio, the bounds on the odds ratio were converted to bounds on the relative risk by using the same weighted average. When there was a zero count, the relative risk was infinite, and thus only the lower confidence bound was of interest. Results for an unstratified analysis were similar.

As a secondary analysis, exact tests were used to compare induction agents separately for asthmatic patients and nonasthmatic patients. Another secondary analysis involved linear regression models for airway pressure and end-tidal carbon dioxide.

Results

In the asthmatic group, the three subgroups did not differ with respect to male/female ratio, age, cigarette use, history of active *versus* inactive asthma, and use of antiasthma medications on the day of surgery (table 1). In the nonasthmatic group, the subgroup who received a thiobarbiturate for induction of anesthesia consisted of more women than did the subgroup receiving the oxybarbiturate (table 1), but the three subgroups did not differ with respect to age and cigarette use (table 1). Fifty-four of the 59 patients in the asthma group had active asthma, 27 of whom were taking antiasthma medications chronically. The numbers of asthmatic patients in each subgroup who received corticosteroids, cromolyn, inhaled β-adrenergic agonists, and theophylline chronically did not differ (table 2). Twenty-seven of the patients with active asthma were taking medications only intermittently for their disease and took no medications on the day of scheduled surgery. Sixteen of these 27 patients used β-adrenergic agonists, 2 used theophylline, and 2 used over-the-counter medications on an occasional basis. The numbers of asthmatic patients in each subgroup who received drugs intermittently did not differ.

Overall, 21 of the 155 patients wheezed after induction of anesthesia and intubation of the trachea (table 3). Of the 21 patients who wheezed, 14 received a thiobarbiturate, and 7 received an oxybarbiturate. The primary analysis examined the common effect of induction agent on wheezing for asthmatic and nonasthmatic patients using a stratified analysis. There was a highly significant ($P < 0.0001$) difference in the incidence of wheezing between patients who received a thiobarbiturate and those who received propofol. Because none of the patients who received propofol wheezed, the relative risk was infinite. In this case, only the lower bound for the 95% confidence, 3.7, is of interest. The incidence of wheezing was significantly different ($P = 0.02$) between patients who received oxybarbiturates and those who received propofol. As before, because none of the patients who received propofol wheezed, the relative risk was infinite, and only the lower bound for the 95% confidence interval, 1.5, is of interest. Lastly, the difference in the incidence of wheezing between patients who received a thiobarbiturate and those who received an oxybarbiturate was of borderline significance ($P = 0.043$). The estimated common relative risk was 1.8, and the 95% confidence interval was 1.02, 4.5.

As a secondary analysis, we examined the incidence of wheezing separately for asthmatic patients and nonasthmatic patients, which gave qualitatively similar results. Fifteen of the 59 asthmatic patients wheezed after induction of anesthesia. Of the 15 asthmatic patients

Table 2. Antiasthma Medication Use in Patients with Active Asthma

	Thiobarbiturate	Oxybarbiturate	Propofol	Total
No. of patients with active asthma	18	21	15	54
No. of patients on medications	10	10	7	27
Medications*				
Corticosteroids				
Inhaled	2	0	4	6
Systemic	2	2	0	4
Inhaled β-agonist	8	7	5	20
Theophylline	3	3	2	8
Cromolyn	1	0	0	1

* Eleven patients received more than one medication.

who wheezed, 9 received a thiobarbiturate, and 6 received an oxybarbiturate (table 3). The incidence of wheezing was significantly different when all three agents were compared in asthmatic patients (P = 0.004). The incidence of wheezing was significantly different between asthmatic patients who received thiobarbiturates and those who received propofol for induction (P = 0.002). In addition, the incidence of wheezing was significantly different between asthmatic patients who received an oxybarbiturate and those who received propofol for induction (P = 0.03). There was no significant difference in wheezing between asthmatic patients who received a thiobarbiturate and an oxybarbiturate for induction (P = 0.16). Six of the 96 nonasthmatic patients wheezed after induction of anesthesia. Of the six nonasthmatic patients who wheezed, five received a thiobarbiturate, and one received an oxybarbiturate (table 3). Because thiopental and thiamylal were both used as thiobarbiturate induction agents in this study, we compared the incidence of wheezing separately in both asthmatic and nonasthmatic patients and found no difference in incidence of wheezing between thiopental and thiamylal. Of the 32 nonasthmatic patients, 21 received thiopental and 11 received thiamylal. Three of the 21 nonasthmatic patients receiving thiopental and 2 of the 11 receiving thiamylal wheezed (P = 0.77). Of the 20 asthmatic patients, 12 received thiopental and 8 received thiamylal. Five of the 12 asthmatic patients who received thiopental wheezed, whereas 4 of the 8 asthmatic patients who received thiamylal wheezed (P = 1.0).

There were no significant differences in the incidence of wheezing between patients at Johns Hopkins and Hadassah hospitals in total (P = 1.0), at 2 min (P = 0.64) or at 5 min (P = 1.0). Six of the 20 asthmatic patients who received a thiobarbiturate wheezed at both 2 and 5 min, 1 wheezed only at 2 min, and 2 wheezed only at 5 min (table 4). Two of the 23 asthmatic patients who received the oxybarbiturate wheezed at both 2 and 5 min, 2 wheezed only at 2 min, and 2 wheezed only at 5 min. None of the 16 asthmatic patients who received propofol for induction wheezed at either 2 or 5 min. Airway pressure, blood

Table 3. Incidence of Wheezing

	Total	Thiobarbiturate	Oxybarbiturate	Propofol
Overall				
No.	21/155	14/52	7/55	0/48
Incidence	14% (8, 19)	27% (15, 39)	13% (4, 22)	0% (0, 6)
Asthmatics				
No.	15/59	9/20	6/23	0/16
Incidence	25% (14, 37)	45% (23, 67)	26% (8, 44)	0% (0, 17)
Nonasthmatics				
No.	6/96	5/32	1/32	0/32
Incidence	6% (1, 11)	16% (3, 28)	3% (0, 9)	0% (0, 9)

Values in parentheses are 95% confidence intervals.

Table 4. Responses in Asthmatic Patients Following Induction of Anesthesia with Thiobarbiturate, Oxybarbiturate, or Propofol

	Thiobarbiturate	Oxybarbiturate	Propofol
No. of subjects	20	23	16
No. of subjects who wheezed			
Overall	9	6	0
2-min	7	4	0
5-min	9	4	0
Airway pressure (cmH_2O)			
2-min	26 ± 2	23 ± 1	18 ± 1*
5-min	25 ± 2	23 ± 1	18 ± 1*
Blood pressure (mmHg)			
Pre-induction	138/84 ± 4/2	139/79 ± 4/3	137/79 ± 6/3
2-min	157/98 ± 6/4	153/94 ± 6/4	128/74 ± 6/6
5-min	129/79 ± 5/4	131/77 ± 4/4	117/71 ± 5/4
End-tidal CO_2 (mmHg)	37 ± 1	36 ± 1	37 ± 1
5-min	35 ± 1	34 ± 1	33 ± 1
Oxygen saturation (%)			
Pre-induction	98 ± .4	99 ± .3	99 ± .3
2-min	99 ± .1	99 ± .2	99 ± .2
5-min	99 ± .2	99 ± .2	99 ± .2

Values are mean ± SEM.

* $P < 0.05$.

pressure, end-tidal carbon dioxide, and oxygen saturation were examined as secondary endpoints. The airway pressure was significantly lower for patients receiving propofol compared to those receiving thiobarbiturate ($P = 0.003$). All instances of wheezing either resolved spontaneously with continued administration of inhalational anesthesia or were successfully treated with a β-adrenergic agonist inhaler 5 min after induction.

Discussion

The results of the current study demonstrate that, in patients as a whole and in asthmatic patients as a subgroup, the incidence of wheezing was significantly less when propofol, rather than a thiobarbiturate or oxybarbiturate, was selected as the induction agent. To our knowledge, relatively few studies have specifically examined the incidence of wheezing during induction of anesthesia in patients either with or without a history of asthma. In one retrospective study of patients with asthma, Shnider and Papper[1] reported a 6.7% incidence of wheezing in patients who received thiopental for induction followed almost immediately by tracheal intubation. In another study conducted in the same period, Gold and Helrich[9] reported an overall incidence of wheezing during general anesthesia of 8.1% (14 of 173 patients). At least 9 of 51 patients who received thiopental for induction in the study by Gold and Helrich wheezed.[9] The higher incidence of overall wheezing seen in asthmatic patients in the current study (25%) is most likely related to the method of data collection and to the more sensitive criteria used for establishing the diagnosis of wheezing. The current study, in contrast to the two previous studies, was prospective, not retrospective. Moreover, most instances of wheezing seen in the current study were mild and self-limited. Such episodes of wheezing may not have been noted in an anesthetic record and subsequently analyzed in a chart review. The overall incidence of wheezing in our nonasthmatic patients (6%) was also higher than the 0.17% incidence reported by Olsson,[10] likely related to the same reasons.

More female than male patients were enrolled in this study. Although this may reflect a greater incidence of asthma in females in this population and in this age group,[11] it more likely reflects the surgical population used in this study. A high proportion of our ASA physical status 1 and 2 patients were undergoing gynecologic surgery. The number of asthmatic patients in this study was too small to determine whether the incidence of wheezing differed in asthmatic patients who smoked cigarettes and asthmatic patients who did not or in asthmatic patients chron-

ically treated with asthma medications and untreated asthmatic patients.

It is unlikely that the lower incidence of wheezing among the asthmatic patients who received propofol compared to those who received either barbiturate was related to gender, age, severity of disease, cigarette smoking, or presence of medication, because the three groups were similar in these respects. It is also unlikely that the results obtained in this study were related to a greater depth of anesthesia with propofol than with the barbiturates.[12] Airway pressure, however, was significantly lower in the propofol group. Both fresh gas flow and tidal volume were controlled in all subjects, but the inspired to expired ratio was not. It is unlikely that a systematic bias existed in inspired to expired ratios only in patients who received propofol to account for the lower airway pressure in this group.

The current study is consistent with a number of recent studies and reports suggesting that propofol may have properties beneficial to patients with asthma. Pederson *et al.*[13] showed that propofol can directly relax guinea pig tracheal tissue and, under some circumstances, was more potent than ketamine. Cigarini *et al.*[14] found that propofol prevented fentanyl-induced bronchoconstriction in surgical patients. Moreover, Pederson[15] reported that propofol, in doses used for sedation, inhibited postoperative bronchospasm in two patients with hyperreactive airway disease.

Both the thiobarbiturate and the oxybarbiturate were associated with an increased incidence of wheezing in patients with asthma. Although we did not find a statistically significant difference in incidence of wheezing between the thiobarbiturate and the oxybarbiturate, it is possible that, had we increased our sample size, a difference, although smaller than originally estimated, may have been detected as *in vitro* studies have suggested.[16] However, the significantly lower incidence of wheezing in the propofol group makes the question of a difference in incidence of wheezing between thiobarbiturate and oxybarbiturate induction agents less important.

In summary, the current study shows that the incidence of wheezing was significantly greater in asthmatic patients receiving a barbiturate for induction of anesthesia than similar asthmatic patients given propofol. This study suggests that propofol should be considered when asthmatic patients require intravenous induction agents and timely tracheal intubation.

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