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Atracurium Versus *Vecuronium in Asthmatic Patients*

A Blinded, Randomized Comparison of Adverse Events

James E. Caldwell, M.B.Ch.B., Marie Lau, B.S.,† Dennis M. Fisher, M.D.‡*

Background: **To determine which of atracurium or vecuronium is associated with fewer adverse cardiovascular and pulmonary events in high-risk patients, the authors administered these drugs to patients with known asthma.**

Methods: **Sixty patients aged 18–75 yr taking bronchodilators chronically for asthma were anesthetized with midazolam, fentanyl, nitrous oxide, and isoflurane; the trachea was intubated without paralysis. When anesthetic conditions and mechanical ventilation were stable, patients were randomly given 0.5 mg/kg atracurium or 0.1 mg/kg vecuronium over 5–10 s, and a blinded observer recorded cardiovascular, pulmonary, and cutaneous signs of adverse reactions for 6 min.**

Results: **Arterial pressures and heart rate decreased after atracurium, and systolic pressure and heart rate decreased with vecuronium; these changes were small in magnitude. Cardiovascular effects (decrease in blood pressure or change in heart rate) >10% were common with both atracurium (60% of patients) and vecuronium (57%). Cardiovascular effects >20% were more frequent with atracurium (37%) than with vecuronium (13%, $P < 0.05$). The incidence of noncardiovascular adverse events (increase in peak airway pressure >5 cmH_2O, tidal volume decrease >10%, rashes, and wheezing) did not differ between atracurium (17%) and vecuronium (7%). The largest increase in peak airway pressure was 5.1 cmH_2O in a patient whose tidal volume decreased 16% with vecuronium; in the remaining patients, tidal volume decreased <10%. No patients experienced inspiratory wheezing, marked decreases in arterial oxygen saturation, or marked increases in end-tidal carbon dioxide tension.**

Conclusions: **The authors conclude that, in patients with asthma, adverse cardiovascular events are more common with atracurium than with vecuronium. (Key Words: Complications: cardiovascular; pulmonary. Diseases: asthma. Neuromuscular relaxants: atracurium; vecuronium.)**

INITIAL clinical trials of atracurium revealed that doses of 0.5–0.6 mg/kg frequently produced cutaneous flushing and hypotension.[1] Although bronchospasm was not observed, because these adverse effects were considered to result from histamine release, atracurium's manufacturer (Burroughs Wellcome, Research Triangle Park, NC) excluded asthmatics from some clinical trials[2] and recommended caution in the dose and rate of administration of atracurium to subjects at high risk for complications related to histamine release.§ Despite concerns about atracurium's cardiovascular effects and its potential for inducing bronchospasm, two reports comparing the incidence of adverse effects after atracurium and either vecuronium or a variety of muscle relaxants concluded that atracurium was associated with either a similar or lower incidence of complications.[3,4] However, neither study focused on or identified patients with known asthma, a group likely to be at high risk for atracurium-related adverse effects.[5,6] In addition, both reports were retrospective, nonblinded, and nonrandomized, leading to our concern that they might have been biased. Therefore, we performed a prospective, blinded, randomized study in known asthmatic patients comparing atracurium to vecuronium.

Methods

After approval by the UCSF Committee on Human Research, 61 patients consented to participate in the study. All patients were ASA physical status 2, had known asthma (defined by a history of bronchospasm

* Associate Professor of Anesthesia.

†Staff Research Associate.

‡Professor of Anesthesia and Pediatrics.

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Address correspondence to Dr. Fisher: Department of Anesthesia, University of California Medical Center, San Francisco, California 94143-0648. Address electronic mail to: fisher@zachary.ucsf.edu.

§Package insert for Tracrium (atracurium). Research Triangle Park: Burroughs Wellcome, 1989.

responsive to bronchodilators), and took bronchodilators (either aminophylline, theophylline, terbutaline, or inhaled agents) chronically. None of the patients were experiencing an acute exacerbation of their asthma. Patients were permitted to take their usual medication until immediately before induction of anesthesia. Patients were excluded from the study if they exceeded 140% of ideal body weight.

General anesthesia was induced with 0.2 mg/kg midazolam, 5 μg/kg fentanyl, 60% N_2O, and increasing concentrations of isoflurane (up to 4% inspired concentration). Tracheal intubation was accomplished without the aid of muscle relaxants. After tracheal intubation, anesthetic concentrations were adjusted, aiming to maintain end-tidal concentrations of 60% N_2O and 0.5%–1.0% isoflurane. Isoflurane concentration was adjusted as necessary to maintain anesthesia and appropriate cardiovascular parameters. The lungs were mechanically ventilated using a Servo 900C ventilator (Siemens-Elema, Solna, Sweden) with an inspiratory time of 1.5 s. Exhaled tidal volume, measured with a Wright respirometer (Boehringer, Wynnewood, PA) placed at the endotracheal tube, was adjusted to approximately 10 ml/kg. Respiratory rate was adjusted aiming to achieve an end-tidal carbon dioxide tension ($P_{ET_{CO_2}}$) in the range 25–40 mmHg.

When anesthetic conditions, airway pressures, blood pressure, heart rate, and $P_{ET_{CO_2}}$ were constant for 5–10 min, 0.5 mg/kg atracurium or 0.1 mg/kg vecuronium was administered over 5–10 s. During the observation period, anesthetic concentrations and ventilation were not adjusted, and no surgery was performed. A blinded observer recorded heart rate; systolic, diastolic, and mean arterial blood pressure (Dinamap, Critikon, Tampa, FL); Sp_{O_2} (N200, Nellcor, Hayward, CA), $P_{ET_{CO_2}}$ and anesthetic concentrations (Datex PB254, Puritan-Bennett, Tewksbury, MA); exhaled tidal volume; and peak airway pressure (Servo 900C) before and at 1, 2, 4, and 6 min after administration of the muscle relaxant. The lungs were auscultated for inspiratory and/or expiratory wheezes, and the skin was observed for rashes or wheals at these time intervals.

For each group, repeated-measures analysis of variance or its nonparametric equivalent, Friedman's test, was used to determine whether values for blood pressure, heart rate, $P_{ET_{CO_2}}$, tidal volume, or peak airway pressure changed over time; differences between groups for baseline values were determined using unpaired *t* tests.

Decreases in blood pressure or changes in heart rate were categorized as >10%, >20%, or >40%. Noncardiovascular adverse effects were an increase in peak airway pressure >5 cmH_2O, a >10% decrease in tidal volume, rash, wheezing, or a >5% decrease in Sp_{O_2}. The incidence of cardiovascular (blood pressure or heart rate) events and noncardiovascular adverse events was compared between groups using chi-square analysis with Yate's continuity correction or Fisher's exact test. For all statistical comparisons, $P < 0.05$ was considered significant.

Results

One patient experienced severe bronchospasm during induction of anesthesia, and the protocol was abandoned; this patient was not assigned to either muscle relaxant group. The two groups were similar in number, weight, height, and gender distribution (table 1); patients given atracurium were older. Baseline values for nitrous oxide and isoflurane concentrations; $F_{I_{O_2}}$; $P_{ET_{CO_2}}$; systolic, diastolic, and mean blood pressures; heart rate; peak airway pressure; and tidal volume were similar for the two groups (table 2). For the atracurium group, nitrous oxide increased and isoflurane decreased during the 6 min after muscle relaxant administration. For both groups, $P_{ET_{CO_2}}$ decreased over time. For atracurium, systolic, diastolic, and mean blood pressure and heart rate decreased; for vecuronium, systolic blood pressure and heart rate decreased. Peak airway pressure increased with vecuronium; tidal volume increased with atracurium.

The incidence of cardiovascular effects >10% was similar with atracurium and vecuronium (table 3). Heart rate changes >10% were more common with vecuronium, although the difference did not attain sta-

Table 1. Demographic Data for Asthmatic Patients Given 0.5 mg/kg Atracurium or 0.1 mg/kg Vecuronium

	Atracurium	Vecuronium
n	30	30
Age (yr, mean ± SD)*	46 ± 13	39 ± 13
Weight (kg, mean ± SD)	73 ± 15	70 ± 15
Height (cm, mean ± SD)	169 ± 9	172 ± 14
Gender (males/females)	12/18	8/22

* $P < 0.05$ between groups.

Table 2. Respiratory and Cardiac Parameters in Asthmatic Patients Given 0.5 mg/kg Atracurium or 0.1 mg/kg Vecuronium

	Before	After Administration of Muscle Relaxant (min)			
		1	2	4	6
Atracurium					
Nitrous oxide (%)*	57 ± 8	58 ± 7	58 ± 7	59 ± 7	59 ± 7
Isoflurane (%)*	0.78 ± 0.30	0.75 ± 0.27	0.76 ± 0.28	0.75 ± 0.28	0.75 ± 0.29
$F_{I_{O_2}}$ (%)	38 ± 7	38 ± 7	38 ± 7	38 ± 7	38 ± 7
$P_{ET_{CO_2}}$ (mmHg)*	32 ± 5	31 ± 4	30 ± 4	29 ± 4	29 ± 4
Blood pressure (mmHg)*					
Systolic	95 ± 16	90 ± 15	87 ± 13	88 ± 13	88 ± 12
Diastolic	54 ± 11	50 ± 11	49 ± 12	48 ± 10	48 ± 10
Mean	69 ± 11	64 ± 12	64 ± 12	64 ± 12	64 ± 11
Heart rate (beats/min)*	78 ± 16	76 ± 17	76 ± 17	75 ± 17	74 ± 16
Peak airway pressure (cmH_2O)	26 ± 8	26 ± 9	26 ± 9	26 ± 9	26 ± 9
Tidal volume (ml)*	742 ± 158	748 ± 157	752 ± 158	755 ± 160	751 ± 159
Vecuronium					
Nitrous oxide (%)*	54 ± 17	55 ± 17	55 ± 17	55 ± 17	55 ± 17
Isoflurane (%)*	0.81 ± 0.27	0.81 ± 0.29	0.78 ± 0.28	0.79 ± 0.29	0.78 ± 0.30
$F_{I_{O_2}}$ (%)	42 ± 17	42 ± 17	42 ± 17	42 ± 17	42 ± 17
$P_{ET_{CO_2}}$ (mmHg)*	31 ± 5	30 ± 5	30 ± 5	29 ± 5	29 ± 5
Blood pressure (mmHg)					
Systolic*	91 ± 10	89 ± 13	88 ± 14	86 ± 13	91 ± 12
Diastolic	50 ± 9	51 ± 13	48 ± 10	49 ± 11	51 ± 12
Mean	64 ± 10	66 ± 16	65 ± 12	63 ± 12	66 ± 12
Heart rate (beats/min)*	73 ± 13	70 ± 13	70 ± 13	69 ± 13	70 ± 13
Peak airway pressure (cmH_2O)*	24 ± 7	25 ± 7	24 ± 7	25 ± 7	25 ± 7
Tidal volume (ml)	720 ± 127	718 ± 122	720 ± 129	723 ± 123	718 ± 123

Values are mean ± SD.

* Values differ over time by repeated-measures ANOVA or Friedman's test.

tistical significance ($P = 0.14$). Decreases in blood pressure >20% and cardiovascular changes >20% were more common with atracurium than with vecuronium.

The incidence of noncardiovascular adverse events was similar for the two muscle relaxants. No patients experienced urticaria or increases in $P_{ET_{CO_2}}$. With one exception described later, there were no increases in peak airway pressure >5 cmH_2O or decreases in tidal volume >10%. Only two patients had decreases in Sp_{O_2} >2%: in one given atracurium, Sp_{O_2} decreased from 100% to 97%, and in another given vecuronium, Sp_{O_2} decreased from 94% to 90%.

Four patients experienced cardiovascular changes >40%. Three of these, all given atracurium, experienced transient hypotension not requiring treatment. For example, in a 64-yr-old woman given atracurium, blood pressure decreased from 128/72 mmHg before atracurium to 42/37 mmHg at 1 min, then returned to 88–92/60–65 mmHg for subsequent measurements. There was no significant change in heart rate and no wheezing or rash, and no additional therapies were instituted. The remaining severe cardiovascular event occurred in a 75-yr-old man given vecuronium: blood pressure decreased from 95/51 to 47/28 mmHg at 4 min, he experienced slight expiratory wheezes, peak airway pressure increased 5.1 cmH_2O, and tidal volume decreased 16%. Heart rate did not change. After 10 mg ephedrine, all values returned to control, and wheezing ceased. No other patients received vasoactive drugs during the study.

Discussion

Initial clinical trials with 0.5 mg/kg atracurium documented decreases in blood pressure and erythematous rashes, adverse effects that were attributed to histamine release.[1] These adverse effects lessened when atracurium was administered slowly or after administration of histamine-blocking agents.[7] Although bronchospasm was not reported, asthmatic patients were excluded from some clinical trials,[2] and Burroughs Wellcome recommended in the pack-

Table 3. Percent of Patients Who Experienced Adverse Effects after 0.5 mg/kg Atracurium or 0.1 mg/kg Vecuronium

	Atracurium (n = 30)	Vecuronium (n = 30)
Heart rate changes		
>10%	17	33
>20%	3	3
>40%	0	0
Blood pressure (systolic, diastolic, or mean) decreases		
>10%	57	37
>20%*	37	10
>40%	10	3
Cardiovascular changes (heart rate or blood pressure)		
>10%	60	57
>20%*	37	13
>40%	10	3
Noncardiovascular changes		
Peak airway pressure increase >5 cm H_2O	0	3
Tidal volume decrease >10%	0	3
Rashes (erythema only)	10	0
Wheezing (expiratory only)	10	7
Decrease in Sp_{O_2} >5%	0	0
Any of these noncardiovascular changes	17	7

* $P < 0.05$ by chi-square with the Yate's continuity correction or Fisher's exact test.

age insert, "Special caution should be exercised in administering Tracrium [atracurium] to patients. . .with any history [of] asthma." Histaminoid reactions, such as wheezing, rash, and hypotension, have been reported not only with atracurium[8,9] but with vecuronium.[10,11] To compare the incidence of these and other adverse effects in a large population, Burroughs Wellcome sponsored two studies.[3,4] In one, the incidence of adverse events was slightly but not statistically significantly less with atracurium than with vecuronium.[3] In the other, "The safety profile of atracurium [was] similar to that of the other neuromuscular blocking agents."[4] However, both studies were retrospective chart reviews, and neither was blinded or randomized. We speculate that, if anesthesiologists identified patients at high risk for histamine-related adverse events, they would preferentially administer a muscle relaxant other than atracurium. If these patients received other anesthetic drugs such as *d*-tubocurarine[12] or morphine[13] that are known to provoke histamine release and precipitate bronchospasm and hypotension, the study would favor atracurium. In addition, neither study focused on or was limited to patients at high risk, *e.g.*, those with asthma. Thus, to determine whether adverse events are equally common with atracurium and other muscle relaxants in patients at high risk from histamine release, it is necessary to perform a prospective, blinded, randomized study in known asthmatic patients.

We observed a frequent occurrence of minor (>10%) cardiovascular events with atracurium and vecuronium; however, because of the small magnitude of these changes, they probably are not of clinical importance. Included in these are small decreases in heart rate with vecuronium (33% of patients), a finding previously described in nonasthmatic patients.[14] Moderate (>20%) decreases in blood pressure occurred more frequently with atracurium than with vecuronium. In most instances, atracurium-induced hypotension was transient and did not require treatment. These transient decreases in blood pressure have been observed in nonasthmatic patients[1] and have been attributed to the release of histamine.[6]

Of the severe adverse reactions, one occurred with vecuronium. The previous stability of that patient's anesthetic course and the temporal relationship of these changes to administration of vecuronium (changes began <2 min after drug administration and peaked at 4 min) suggests that the changes resulted from vecuronium. Thus, like atracurium, vecuronium can—on rare occasions—trigger severe histaminoid reactions.

Several issues of our study design warrant comment. First, although histamine release is the likely mecha-

nism for atracurium-induced hypotension,[6] we did not measure histamine concentrations. Our decision not to measure histamine concentrations resulted from our interest in the incidence and severity of adverse events rather than in assigning a mechanism to those events. Had histamine concentrations increased in the absence of adverse events, the significance of the histamine concentrations would have been questioned. Conversely, had adverse events occurred in concert with increased histamine concentrations, the incremental value of the histamine concentrations would have been small. Thus, changes in histamine concentration represent a surrogate outcome[15] for our issue of interest, the incidence of adverse events with these two muscle relaxants.

Second, we compared adverse effects of the muscle relaxants by assessing clinical measures of pulmonary function, such as $P_{ET_{CO_2}}$ and peak airway pressure, during stable mechanical ventilation rather than measure pulmonary compliance. Because we ventilated the patients' lungs using a volume-control mode, a small change in pulmonary compliance should increase peak airway pressure rather than change tidal volume. However, a larger increase in peak airway pressure would increase wasted ventilation in the breathing circuit, thereby reducing tidal volume. To eliminate the confounding factor of compliance of the breathing circuit, we measured tidal volume at the endotracheal tube, thereby measuring true changes in tidal volume.

Third, our study design differs from one form of clinical practice in which either thiopental or propofol is given to induce anesthesia, and a muscle relaxant is given immediately thereafter. We selected our design because other investigators[16] have shown that induction of anesthesia is associated with a decrease in arterial pressure and tracheal intubation with an increase. Therefore, to determine the specific contribution of muscle relaxants to hemodynamic changes, administration of these drugs must be temporally separated from those other hemodynamically disruptive events. In addition, because thiopental provokes wheezing in a large proportion (42%) of patients with asthma,[17] its administration would confound interpretation of histaminoid effects related to subsequent administration of atracurium or vecuronium. We contend that the only appropriate means to detect adverse cardiac and pulmonary effects of a muscle relaxant is to administer the muscle relaxant during a period when stimulus is constant (*i.e.,* not before or immediately after tracheal intubation) and cardiovascular effects of other drugs are stable (*i.e.,* not immediately after bolus doses of sedative-hypnotic drugs). In addition, the design of our study is analogous to the clinical situation in which succinylcholine is used to facilitate tracheal intubation, and atracurium or vecuronium is given when the effect of succinylcholine has dissipated. However, we did not administer succinylcholine to facilitate tracheal intubation because it can produce adverse cardiovascular responses and provoke histamine release.[18]

The final issue of study design is the potential influence of the anesthetic drugs on the release of histamine. Halothane, 2% (2.7 MAC) but not 0.5% (0.7 MAC), inhibits histamine release induced by *d*-tubocurarine.[19] Although comparable data do not exist for isoflurane, the mean dose of isoflurane in the current study (0.8% $\approx$0.7 MAC) is similar to the halothane dose that does not inhibit histamine release. Thus, we speculate that isoflurane administration does not confound our study. Midazolam both inhibits[20] and promotes histamine release[21]; thus, its influence on our results is not obvious. We attempted to design an anesthetic technique compatible with patient safety, adequate anesthetic depth for tracheal intubation, and avoidance of awareness, and with minimal affect on histamine release. Although the use of propofol for induction of anesthesia does not provoke wheezing in asthmatic patients,[17] we did not use the drug because it can provoke histamine release[22] and because of evidence that the combination of atracurium and propofol can produce significant adverse effects in atopic patients.[23]

We demonstrated that moderate cardiovascular events were more common with atracurium than with vecuronium. Although a similar trend existed for severe cardiovascular events (a threefold increase for atracurium compared to vecuronium), this difference did not attain statistical significance. Power analysis reveals that a sample of more than 300 individuals—far larger than the current study—would be necessary to demonstrate statistical significance if the true incidence of severe cardiovascular events were 10% with atracurium and 3% with vecuronium.

Few prospective clinical trials have examined the influence of anesthetic technique on outcome of asthmatic patients. Recently, Pizov *et al.*[17] reported in a randomized, prospective, blinded study of asthmatic patients that wheezing was common when anesthesia was induced with barbiturates (42% with thiopental, 26% with methohexital, and 50% with thiamylal) but rare with propofol (0 of 16 patients). Our study examines another set of drugs commonly used during anesthesia and suggests

that moderate cardiovascular events are more common with atracurium than with vecuronium. Our findings suggest that atracurium may not be the optimal muscle relaxant for patients with asthma.

In summary, in patients with known asthma, minor cardiovascular effects were common after administration of either atracurium or vecuronium, but no patient experienced significant increases in airway pressure or decreases in arterial oxygen saturation. Moderate cardiovascular events were more common with atracurium than with vecuronium. However, severe adverse events, such as those requiring therapeutic intervention, are uncommon when either atracurium or vecuronium is given to asthmatic patients anesthetized with nitrous oxide and isoflurane.

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