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Efficacy of Propofol to Prevent Bronchoconstriction

Effects of Preservative

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Background: **The authors previously showed that propofol attenuates bronchoconstriction. Recently, a newer formulation of propofol with metabisulfite preservative has been introduced. metabisulfite causes airway narrowing in asthmatics. Therefore, we tested whether the preservative metabisulfite abolishes the ability of propofol to attenuate bronchoconstriction. The authors used a sheep model in which anesthetic agents could be directly administered to the airways *via* the bronchial artery.**

Methods: **After Internal Review Board approval, seven sheep were anesthetized (pentobarbital 20 mg · kg^{-1} · h^{-1}) and paralyzed (pancuronium 2 mg), and the lungs were ventilated. After left thoracotomy, the bronchial artery was cannulated and perfused. In random order, propofol with and without metabisulfite, lidocaine (5 mg/ml), or metabisulfite alone (0.125 mg/ml) was infused into the bronchial artery at a rate of 0.06, 0.2, or 0.6 ml/min. After 10 min, airway resistance (R_{aw}) was measured before and after vagal nerve stimulation (30 Hz, 30-ms duration at 30 V for 9 s.) and methacholine challenge (2 μg/ml at 2 ml/min in the bronchial artery). Data were expressed as a percent of maximal response and analyzed by analysis of variance with correction and with significance accepted at $P \leq 0.05$.**

Results: **R_{aw} at baseline was not significantly different among the four drugs ($P = 0.87$). Infusion of lidocaine and propofol without metabisulfite into the bronchial artery caused a dose-dependent attenuation of the vagal nerve stimulation–induced bronchoconstriction ($P = 0.001$). Propofol with metabisulfite had no effect on vagal nerve stimulation–induced bronchoconstriction ($P = 0.40$). There was a significant difference in the ability of propofol without metabisulfite compared with propofol with metabisulfite to attenuate vagal nerve stimulation–induced ($P = 0.0001$) and methacholine-induced bronchoconstriction ($P = 0.0001$).**

Conclusion: **Propofol without metabisulfite and lidocaine attenuated vagal nerve stimulation–induced bronchoconstriction in a dose-dependent fashion. Propofol without metabisulfite also decreased direct airway smooth muscle constriction. The preservative used for propofol can have a dramatic effect on its ability to attenuate bronchoconstriction.**

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IN patients with asthma, tracheal intubation can increase the risk for development of severe bronchospasm. When intubation is necessary, the use of premedications[1–4] and inhalation anesthetics[5–9] may reduce this risk. Moreover, a rapid-acting intravenous induction agent is often necessary to facilitate securing the airway. However, the most effective induction agent for prevention of bronchospasm in patients with asthma is controversial. Compared with thiopental, propofol has been shown to decrease the prevalence of wheezing after induction of anesthesia and intubation of the trachea in healthy and asthmatic patients.[10–12]

Recently, a newer formulation of propofol with metabisulfite preservative has been introduced. metabisulfite has previously been shown to cause airway narrowing in asthmatic subjects.[13,14] However, the combination of propofol and metabisulfite on airway responsiveness has not been determined.

Therefore, we undertook the current study to test the hypothesis that the preservative metabisulfite abolishes the ability of propofol to attenuate bronchoconstriction. We used a sheep model in which we administered the anesthetic agents directly to the airways *via* the bronchial artery.

We found that at clinically relevant concentrations, propofol without metabisulfite and lidocaine attenuated vagally induced airway constriction. Furthermore, metabisulfite alone caused a small increase in airway responsiveness to vagally induced and methacholine-induced airway responsiveness. In addition, propofol with metabisulfite did not attenuate vagally or methacholine-induced bronchoconstriction.

Methods

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Anesthesia was induced in seven sheep (25–35 kg) with intramuscular ketamine (30 mg/kg) and subsequently maintained with pentobarbital sodium (20 mg · kg^{-1} · h^{-1}). Tracheostomy was performed, the sheep were paralyzed with pancuronium bromide (2 mg intravenous, with supplementation during the experiment), and the lungs were mechanically ventilated with room air with supplemental oxygen at a rate of 15 breaths/min and a tidal volume of 12 ml/kg. Five centimeters H_2O positive end-expiratory pressure was applied. The left thorax was opened at the fifth intercostal space and heparin (20,000 units) was administered. The esophageal and thoracic tracheal

branches of the bronchoesophageal artery were ligated as previously described.[15] The bronchial branch was cannulated with an 18-gauge angiocatheter and perfused with a constant flow (0.6 mg · kg^{-1} · h^{-1}) of autologous blood withdrawn from a femoral artery catheter by a variable-speed pump (Gilson, Villiers-Le-Bel, France). Systemic blood pressure, heart rate, and pulmonary bronchial pressure were measured continuously throughout the study.

Airway Resistance

Conducting airway resistance (R_{aw}) was measured by the method of forced oscillation.[16] In this method, a gas volume of approximately 30 ml was oscillated for 1.5 s at a frequency of 9 Hz after each tidal breath. Airway pressure was measured at a side arm of the tracheal cannula, and a flow signal was obtained from a pneumotachograph positioned between the oscillator and the cannula. Oscillatory signals were analyzed with an online computer that measured pressures at points of peak flow. Average resistance was obtained over 8–10 oscillatory cycles. Baseline R_{aw} measured in this manner in anesthetized sheep typically results in a value of 1.0 to 2.0 cm $H_2O \cdot l^{-1} \cdot s^{-1}$, which is close to values reported by others.[17,18]

Airway Reactivity

Intrabronchial Artery Infusion. Airway reactivity was determined by measuring R_{aw} before and after intrabronchial artery infusion of methacholine. Methacholine was delivered through a side-port of the bronchial artery perfusion circuit. From previous experiments, we confirmed that a plateau in the increase in R_{aw} is achieved within 2 min of agonist delivery. Sheep received a continuous infusion of methacholine in a concentration of 2 μg/ml at 1 ml/min through the bronchial artery, which caused an approximately 100% increase in R_{aw}. After a 2-min delivery, the infusion pump was turned off, and the animal's R_{aw} was allowed to recover to prechallenge level.

Vagal Nerve Stimulation. The vagus nerves were isolated and nerve stimulator electrodes were attached bilaterally (Harvard Apparatus, Holliston, MA). After establishing baseline R_{aw}, the vagal nerves were simultaneously stimulated bilaterally (30 Hz, 30 ms duration, 30 V, 9 s) which caused bronchoconstriction and a decrease in heart rate. Both responses rapidly reversed during cessation of stimulation (less than 30 s).

Anesthetic Drugs. Propofol without metabisulfite (AstraZeneca Pharmaceuticals, Wilmington, DE), propofol with metabisulfite (Baxter Pharmaceutical Products Inc, New Providence NJ), and lidocaine (Astra Pharmaceutical Products, Inc., West Borough, MA) were administered in concentrations of 5 mg/ml. metabisulfite alone (Sigma, St. Louis, MO) was administered in a concentration of 0.125 mg/ml, a concentration equal to that in the propofol with metabisulfite solution. Each of the four drugs was delivered through a side port of the bronchial artery perfusion circuit by a dedicated infusion pump upstream from the methacholine infusion site. The infusions rates were 0.06, 0.2, and 0.6 ml/min, rates that were previously calculated to deliver clinically relevant concentrations of intravenous anesthetics to the airway. For propofol, we calculated the molar concentrations to be 8.4×10^{-5}, 2.8×10^{-4}, and 8.4×10^{-4} M, respectively.[19] For lidocaine, we calculated the molar concentrations to be 5.4×10^{-5}, 1.8×10^{-4}, and 5.4×10^{-4} M, respectively.

Protocol

The sheep were anesthetized and underwent ventilation as described previously herein. After a 30-min recovery period (and 2 h after the intramuscular administration of ketamine), baseline R_{aw} was measured, and the airways were constricted first by vagal nerve stimulation (VNS), as described, while R_{aw} was measured. After recovery to baseline (2 to 3 min), methacholine was infused through the bronchial artery and R_{aw} was again measured. After recovery to baseline (3–5 min), in random order, one at a time, the three drugs and metabisulfite were infused into the bronchial artery. After 10 min of infusion at a given rate, the R_{aw} was measured before challenge and during constriction by VNS and methacholine infusion. After recovery from the methacholine administration, the drug was infused at the next higher rate and the airway measurements were repeated. After the final rate of infusion for a specific drug, the sheep were allowed to recover (30–60 min), baseline measurements were repeated, and the next drug was infused.

Analysis

Systemic blood pressure was analyzed by one-way analysis of variance. Baseline stimulation (100%) for each sheep for each drug was defined as the change in R_{aw} with VNS and methacholine before infusion of that specific anesthetic drug into the bronchial artery. Baseline R_{aw} before each drug challenge was analyzed for potential changes in anesthetic level over time by using one-way analysis of variance. The changes in R_{aw} as a percent of baseline stimulation were analyzed separately for each drug by one-way analysis of variance to evaluate whether there was a dose effect. In addition, to test whether there was an effect by the addition of metabisulfite to the propofol, two-way analysis of variance was performed. Scheffè and Bonferroni–Dunn corrections for repeated measured were performed; both methods provided similar results. Significance was considered to be $P \leq 0.05$.

Results

Baseline systemic blood pressure was 117 ± 10/83 ± 10 mm Hg (systolic/diastolic, mean ± SD) and did not

Table 1. Control Airway Resistance in the Baseline State before the Infusion of Each Drug and during the Highest Dose of Drug

Drug	R_{aw} Control (Preinfusion) (cm $H_2O \cdot l^{-1} \cdot s^{-1}$)	R_{aw} (Highest Infusion) (cm $H_2O \cdot l^{-1} \cdot s^{-1}$)	*P* Value
Lidocaine	1.7 ± 0.3	1.1 ± 0.3	0.15
Propofol	2.0 ± 0.3	2.0 ± 0.5	0.93
Propofol + MBS	1.8 ± 0.4	3.0 ± 1.2	0.38
MBS	1.8 ± 0.3	2.2 ± 0.6	0.13

MBS = metabisulfite; R_{aw} = airway resistance.

vary significantly before challenges either by drug (P= 0.80) or by dose (P = 0.37). Baseline R_{aw} was 1.8 ± 0.8 cm $H_2O \cdot l^{-1} \cdot s^{-1}$. Infusion of the three anesthetics and metabisulfite into the bronchial artery did not significantly alter the baseline R_{aw} before each challenge either by dose (P = 0.58) or by drug (P = 0.42, table 1). Over time (first through fourth drug before drug infusion and challenge), we found no difference in the baseline R_{aw} related to the sequence of the measurement. The baseline R_{aw} values were (mean ± SD) 1.9 ± 0.8, 1.6 ± 0.7, 1.8 ± 0.8, 1.9 ± 1.0 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ for the first through the fourth baseline measurements, respectively (P = 0.92). In addition, we analyzed the maximal response to VNS and methacholine before each infusion of anesthetic over time. Again, we found no difference in the maximal response to VNS ($P > 0.28$) and methacholine ($P > 0.49$) related to the sequence of the measurements.

Before anesthetic drug infusion into the bronchial artery, VNS and methacholine caused a significant increase in R_{aw} at baseline (maximum response). Vagal nerve stimulation at baseline increased R_{aw} to (mean ± SD) 4.5 ± 1.9 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ (161 ± 61% of baseline), which was not significantly different among drugs (baseline measured before infusion of each drug into the bronchial artery, P = 0.87). Methacholine increased R_{aw} to 3.0 ± 1.1 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ (174 ± 31% of baseline), which also did not differ among drugs (P = 0.84).

Lidocaine had a significant dose effect on airway responses to stimulation. Lidocaine caused a dose-dependent attenuation in the VNS-induced bronchoconstriction. At lidocaine infusion rates of 0.06, 0.2, and 0.6 ml/min, VNS increased R_{aw} to 76 ± 17, 61 ± 15, and 55 ± 9% of maximum, respectively (fig. 1, $P < 0.001$). As expected, lidocaine, at clinically relevant concentrations had no effect on methacholine-induced airway constriction. At lidocaine infusion rates of 0.06, 0.2, and 0.6 ml/min, methacholine increased R_{aw} to 94 ± 5, 100 ± 7, and 91 ± 18% of maximum, respectively (fig. 2, P = 0.21).

Metabisulfite increased airway responses to stimulation. At metabisulfite infusion rates of 0.06, 0.2, and 0.6 ml/min, during VNS, R_{aw} was 110 ± 17, 113 ± 27, and 116 ± 33% of maximum, respectively (fig. 1, P = 0.66). Likewise, at metabisulfite infusion rates of 0.06, 0.2, and 0.6 ml/min methacholine, R_{aw} was 111 ± 19, 123 ± 33, and 127 ± 38% of maximum, respectively (fig. 2, P = 0.32). Because of greater variance, these increases were not significant compared with baseline.

Propofol without metabisulfite affected VNS- and methacholine-induced bronchoconstriction in a dose-dependent manner. At propofol without metabisulfite infusion rates of 0.06, 0.2, and 0.6 ml/min, VNS increased R_{aw} to 84 ± 15, 71 ± 10, and 58 ± 10% of maximum, respectively (fig. 1, $P < 0.001$). Propofol without metabisulfite attenuated methacholine-induced bronchoconstriction at the highest dose administered. At propofol without metabisulfite infusion rates of 0.06, 0.2, and 0.6 ml/min, methacholine increased R_{aw} to 93 ± 13, 88 ± 17, and 79 ± 19% (P = 0.01) of maximum, respectively (fig. 2).

In contrast with the results of propofol without metabisulfite, propofol with metabisulfite at all doses administered did not attenuate R_{aw} during VNS or infusion of methacholine compared with baseline before infusion. At propofol with metabisulfite infusion rates of 0.06, 0.2, and 0.6 ml/min, VNS increased R_{aw} to 95 ± 8, 98 ± 16, and 87 ± 23% of maximum, respectively (fig. 1, P = 0.40). During methacholine infusion, R_{aw} increased to 106 ± 18, 112 ± 28 and 110 ± 56% at rates of 0.06, 0.2, and 0.6 ml/min, respectively (P = 0.91).

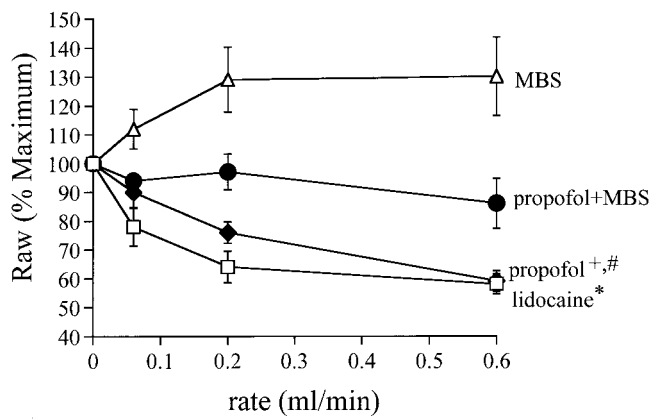

Fig. 1. Airway resistance (R_{aw}) response to vagal nerve stimulation in seven sheep during increased doses of propofol without metabisulfite (MBS; diamonds), propofol with metabisulfite (circles), lidocaine (squares), and metabisulfite alone (triangles). R_{aw} was significantly decreased compared with baseline for all doses of lidocaine. R_{aw} was significantly decreased compared with baseline for all doses of propofol without metabisulfite. R_{aw} was significantly different overall for propofol without metabisulfite compared with propofol with metabisulfite. *$P < 0.01$; +$P < 0.01$; #$P < 0.0001$.

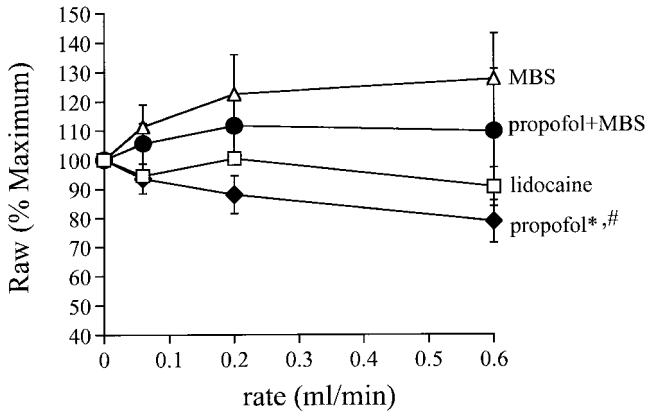

Fig. 2. Airway resistance (R_{aw}) response to methacholine in seven sheep during increased doses of propofol without metabisulfite (MBS; diamonds), propofol with metabisulfite (circles), lidocaine (squares), and metabisulfite alone (triangles). R_{aw} was significantly decreased compared with baseline at the highest dose of propofol without metabisulfite. R_{aw} was significantly different overall for propofol without metabisulfite compared with propofol with metabisulfite. *$P < 0.01$; #$P < 0.02$.

Moreover, when compared with propofol without metabisulfite, the effect of propofol with metabisulfite was significantly different. There was a significant difference in the ability of propofol without metabisulfite compared with propofol with metabisulfite to attenuate VNS-induced bronchoconstriction ($P = 0.0001$). Likewise, there was a significant difference in the ability of propofol without metabisulfite compared with propofol with metabisulfite to attenuate methacholine-induced bronchoconstriction ($P = 0.0001$).

Discussion

Our results show that propofol with metabisulfite does not attenuate either VNS- or methacholine-induced airway constriction compared with propofol without metabisulfite. Furthermore, metabisulfite seems to have effects through neural and direct airway smooth muscle mechanisms.

Because it was necessary that the animals be anesthetized during the study, we used a continuous infusion of pentobarbital to maintain anesthesia. Although any anesthetic can have some effect on airway responses, compared with the responses in unanesthetized animals, we chose pentobarbital because it has been shown not to have significant affects on airway reactivity at maintenance doses.[20] Our laboratory previously showed that barbiturate thiopental did not influence airway responsiveness to VNS- or methacholine-induced bronchoconstriction.[19] Also, continuous infusion was used to maintain a constant depth of anesthesia. Because the anesthetic drug challenges were randomized, any changes in depth of anesthesia over time would also be random and would not have biased the results. Furthermore, we found no difference in baseline R_{aw} before challenge during the duration of the study or during VNS and methacholine infusion before anesthetic drug infusion. Again suggesting that there was no confounding by time caused by either the intramuscular ketamine at induction of anesthesia or the heparinization for cannulation of the bronchial artery.

We chose concentrations of anesthetic drugs that would be clinically relevant.[19] In a recent study, Ludbrook *et al.*[21] evaluated the rate of intravenous administration of propofol on peak arterial levels of propofol. When 100 mg propofol was administered at 200 mg/min, a peak brain arterial concentration of 30 μg/ml was measured. Therefore, the doses we used seem to be clinically relevant as measured by doses for induction of anesthesia in sheep. We chose a concentration of metabisulfite based on the concentration currently used as a preservative in the commercially available propofol formulation. Therefore, the concentration of metabisulfite alone was the same as the concentration of metabisulfite in the propofol with metabisulfite anesthetic solution.

The primary goal of this study was to determine the effects of the preservatives used in commercially available propofol anesthetics. Previous work from our laboratory and other investigators showed that propofol without metabisulfite attenuated bronchoconstriction in an animal model[19] and in humans.[10–12] Recent availability of propofol that uses metabisulfite as a preservative raised questions about the combined effect of the two agents on airway responsiveness. Our results clearly show that the addition of the preservative metabisulfite to propofol abolishes the attenuation of propofol on induced bronchoconstriction. Propofol with metabisulfite was clearly not effective at preventing VNS-induced bronchoconstriction (fig. 1). This is in contrast with propofol without metabisulfite, which significantly attenuated VNS-induced bronchoconstriction (fig. 1). Furthermore, the preservative metabisulfite also affected the responsiveness of the airways to methacholine-induced direct airway smooth muscle stimulation. Propofol with metabisulfite caused a slight but not significant increase in R_{aw} to methacholine-induced bronchoconstriction (fig. 2). In contrast, propofol without metabisulfite attenuated methacholine-induced bronchoconstriction (fig. 2).

We chose lidocaine as a positive control for VNS-induced bronchoconstriction. As expected, lidocaine was effective at attenuating VNS-induced bronchoconstriction. It was interesting that the lidocaine, even at the highest dose administered, only blocked about one half of the increase in R_{aw} induced by VNS (fig. 1). Although higher doses may have been more effective, they would not have been clinically relevant. The VNS parameters used were presumably supraphysiologic. This probably accounts for the inability of the lidocaine, in clinically relevant doses, to completely block the VNS-induced bronchoconstriction. In addition, the ability of propofol without metabisulfite and lidocaine were similar in their ability to block VNS-induced bronchoconstriction.

Another goal of our study was to determine the mechanism of metabisulfite-induced airway hyperresponsiveness. Previous studies have shown that metabisulfite induces increased airway responsiveness in animals[14] and humans.[13] Because of the similarity of the airway response to the VNS- and methacholine-induced bronchoconstriction during metabisulfite infusion, our results suggest that metabisulfite affects are through direct airway smooth muscle mechanisms to cause airway hyperresponsiveness.

The effects of propofol at preventing induced bronchoconstriction have been more extensively evaluated. *In vitro* studies[22–26] and *in vivo* studies in animals[19] and in humans[27,28] both have shown that propofol is able to attenuate the response to a variety of bronchoconstrictor agents. Consistent with these previous studies, our results also show that propofol without metabisulfite, but not propofol with metabisulfite, was able to attenuate induced airway constriction. We found that propofol reduced the VNS-induced increase in R_{aw} in a dose-dependent fashion. Although we did not observe complete prevention of the VNS-induced increase in R_{aw}, this may be a result of the doses administered or of protein binding. We chose to administer doses that would be achieved clinically during induction of anesthesia.[21] Furthermore, consistent with previous work from our laboratory,[19] propofol had limited effectiveness against methacholine-induced increases in R_{aw}.

Our findings of a similar ability of propofol without metabisulfite and lidocaine to attenuate VNS-induced bronchoconstriction suggest a common neural pathway to attenuate VNS-induced bronchoconstriction. Our current results also support our previous findings[19] and the findings of other investigators[29] who have evaluated the mechanisms for neural depression by propofol. Biddle *et al.*[29] evaluated the effects of propofol on the neural responses in a rat artery smooth muscle preparation. They found that propofol attenuated the response to exogenous norepinephrine and the response to endogenous norepinephrine release from nerve terminals induced by electrical field stimulation. However, any direct effect of the drugs on smooth muscle would also inhibit neurally mediated bronchoconstriction. In addition, it was interesting that we observed a suggestion of a decrease in baseline airway tone with lidocaine administration but not with propofol without metabisulfite.

In summary, propofol without metabisulfite attenuated induced bronchoconstriction. Propofol without metabisulfite attenuated neurally mediated and direct airway smooth muscle–induced bronchoconstriction. In contrast, propofol with metabisulfite attenuated neither neural- nor direct airway smooth muscle–induced bronchoconstriction. The preservative used for propofol can have a dramatic effect on its ability to attenuate bronchoconstriction.

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