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Mechanisms of Bronchoprotection by Anesthetic Induction Agents

Propofol versus *Ketamine*

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Background: **Propofol and ketamine have been purported to decrease bronchoconstriction during induction of anesthesia and intubation. Whether they act on airway smooth muscle or through neural reflexes has not been determined. We compared propofol and ketamine to attenuate the direct activation of airway smooth muscle by methacholine and limit neurally mediated bronchoconstriction (vagal nerve stimulation).**

Methods: **After approval from the institutional review board, eight sheep were anesthetized with pentobarbital, paralyzed, and ventilated. After left thoracotomy, the bronchial artery was cannulated and perfused. In random order, 5 mg/ml concentrations of propofol, ketamine, and thiopental were infused into the bronchial artery at rates of 0.06, 0.20, and 0.60 ml/min. After 10 min, airway resistance was measured before and after vagal nerve stimulation and methacholine given *via* the bronchial artery. Data were expressed as a percent of baseline response before infusion of drug and analyzed by analysis of variance with significance set at $P \leq 0.05$.**

Results: **Systemic blood pressure was not affected by any of the drugs ($P > 0.46$). Baseline airway resistance was not different among the three agents ($P = 0.56$) or by dose ($P = 0.96$). Infusion of propofol and ketamine into the bronchial artery caused a dose-dependent attenuation of the vagal nerve stimulation–induced bronchoconstriction to 26 ± 11% and 8 ± 2% of maximum, respectively ($P < 0.0001$). In addition, propofol caused a significant decrease in the methacholine-induced bronchoconstriction to 43 ± 27% of maximum at the highest concentration ($P = 0.05$)**

Conclusions: **The local bronchoprotective effects of ketamine and propofol on airways is through neurally mediated mechanisms. Although the direct effects on airway smooth muscle occur at high concentrations, these are unlikely to be of primary clinical relevance. (Key words: Airways; bronchial circulation; methacholine; vagal.)**

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INDUCTION of anesthesia and intubation of the trachea causes airway constriction. In patients with asthma, tracheal intubation can increase the risk for development of severe bronchospasm. When intubation is required, the use of premedications[1–4] and inhalational anesthetic agents[5–9] may reduce this risk. Moreover, a rapid acting intravenous induction agent is often required to facilitate securing the airway. The most effective induction agent for prevention of bronchospasm in patients with asthma remains controversial, however. Two intravenous induction agents, propofol and ketamine, have been purported to decrease the risk of bronchospasm on induction of anesthesia and intubation. Propofol has been shown to decrease the prevalence of wheezing after induction of anesthesia and intubation of the trachea in normal and asthmatic patients compared with thiopental.[10–12] Likewise, ketamine has been shown to be effective at preventing and actually reversing wheezing in patients with asthma who require anesthesia and intubation.[13,14]

It is generally presumed that the major mechanism of action of ketamine on airways *in vivo* is through indirect actions by prevention of the reuptake of circulating catecholamines, which leads to bronchodilation.[15] *In vitro* data have suggested that ketamine and propofol have direct airway smooth muscle relaxant effects[16–21] and neural effects.[22–26] Whether these mechanisms are

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important *in vivo* have not been determined. Therefore, we undertook the current study to examine the local airway effects of propofol and ketamine on attenuating direct and reflex induced airway constriction. We used a sheep model in which we could administer the anesthetic agents directly to the airways *via* the bronchial artery.

We found that at clinically relevant concentrations, ketamine and propofol diminished vagally induced airway constriction compared with thiopental. Further, propofol also decreased the direct effects of methacholine on airway smooth muscle, but this only occurred at the highest dose administered. Therefore, these data demonstrate that the local bronchoprotective effects of ketamine and propofol on airways is through neurally mediated mechanisms. Although direct effects on airway smooth muscle occur at high concentrations, these effects are unlikely to be of primary clinical relevance.

Methods

General

Our study protocol was approved by The Johns Hopkins Animal Care and Use Committee. Anesthesia was induced in eight sheep (25–35 kg) with intramuscularly administered ketamine (30 mg/kg) and subsequently maintained with pentobarbital sodium (20 $mg \cdot kg^{-1} \cdot h^{-1}$). A tracheostomy was performed, the sheep were paralyzed with pancuronium bromide (2 mg intravenously, 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 of H_2O positive end-expiratory pressure was applied. The left thorax was opened at the fifth intercostal space, and heparin (20,000 U) was administered. The esophageal and thoracic tracheal branches of the bronchoesophageal artery were ligated as previously described.[27] The bronchial branch was then cannulated with an 18-gauge angiocatheter and perfused with a constant flow (0.6 $ml \cdot min^{-1} \cdot kg^{-1}$) 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 bronchial arterial pressure were measured continuously throughout the study.

Airways Resistance

Conducting airways resistance (R_{aw}) was measured by forced oscillation.[28] In this method, a gas volume of ≈30 ml is oscillated for 1.5 s at a frequency of 9 Hz after each tidal breath. Airway pressure is measured at a side arm of the tracheal cannula, and a flow signal is obtained from a pneumotachograph positioned between the oscillator and the cannula. Oscillatory signals are analyzed with an on-line computer that measures pressures at points of peak flow. An average resistance is obtained over 8–10 oscillatory cycles. Baseline R_{aw} measured in this manner in anesthetized sheep typically results in a value of 1.0–2.0 cm $H_2O \cdot l^{-1} \cdot s^{-1}$, which is close to values reported by others.[29,30]

Airways Reactivity

Intrabronchial Artery Infusion. Airways reactivity was determined by measuring R_{aw} before and after intrabronchial artery infusion of methacholine. Methacholine was delivered through a sideport of the bronchial artery perfusion circuit. From previous experiments, we have 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 1–2 μg/ml at 2 ml/min through the bronchial artery, which caused an ≈100% increase in R_{aw}. With a nominal bronchial artery perfusion rate of 20 ml/min, this delivery rate resulted in calculated molar concentration between 5×10^{-7} M to 10^{-6} M methacholine. After a 2-min delivery, the infusion pump was turned off and the animal 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, 40 V, 9 s), which caused bronchoconstriction and a decrease in heart rate. Both of these responses rapidly reversed on cessation of stimulation (<30 s).

Protocol

The sheep were anesthetized and ventilated as described earlier. After a 30-min recovery period (and 2 h after the intramuscularly administered 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 (2–3 min), methacholine was infused through the bronchial artery and R_{aw} was measured again. After recovery to baseline (3–5 min), in random order, the three anesthetic agents were infused into the bronchial artery. The concentration for all the drugs was 5 mg/ml, and the infusion rates

were 0.06, 0.20, and 0.60 ml/min. After 10 min of infusion at a each rate, the R_{aw} was measured prechallenge and during constriction by VNS and infusion of methacholine. After recovery, the next rate was infused and the airway measurements 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

The concentration of anesthetic drug in the bronchial circulation was calculated. With a controlled infusion of autologous blood into the bronchial artery at 20 ml/min, and the infusion rates of 0.06, 0.20, and 0.60 ml/min of anesthetic drugs into the perfusate, we calculated the molar concentrations of thiopental to be 5.6×10^{-5} M, 1.9×10^{-4} M, and 5.6×10^{-4} M, respectively. Likewise for propofol, we calculated the molar concentrations to be 8.4×10^{-5} M, 2.8×10^{-4} M, and 8.4×10^{-4}, respectively. For ketamine, the calculated molar concentrations were 5.4×10^{-5} M, 1.8×10^{-4} M, and 5.4×10.0^{-4} M, respectively.

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. The changes in R_{aw} as a percent of baseline stimulation were analyzed separately for each drug by one-way analysis of variance, with Bonferroni correction for repeated measures within the sheep. The effective dose that caused a 50% decrease in baseline response (ED_{50}) was calculated along the linear part of the dose–response curves (first dose to third dose) for ketamine and propofol for the VNS and methacholine challenge each sheep. The means of the ED_{50} values were compared for each challenge by paired *t* test. Statistical significance was considered to be $P \leq 0.05$.

Results

Baseline systemic blood pressure was 119 ± 15/88 ± 16 (systolic/diastolic mean ± SD) and did not vary significantly during challenges either by drug ($P = 0.92$) or by dose ($P = 0.38$). Baseline R_{aw} was 1.95 ± 0.14 cm $H_2O \cdot l^{-1} \cdot s^{-1}$. Infusion of the three anesthetic agents into the bronchial artery did not significantly alter the baseline R_{aw} before each challenge either by dose ($P = 0.88$) or by drug ($P = 0.83$) (table 1). Further, before infusion of anesthetic drug, VNS and methacholine caused a significant increase in R_{aw} at baseline (maximum response). Vagal nerve stimulation at baseline increased R_{aw} to 5.61 ± 0.53 cm $H_2O \cdot l^{-1} \cdot s^{-1}$ (mean ± SEM), which was not significantly different among drugs ($P = 0.93$). Methacholine increased R_{aw} to 3.46 ± 0.18 cm $H_2O \cdot l^{-1} \cdot s^{-1}$, which also did not differ among drugs ($P = 0.59$).

Table 1. Baseline Raw (cm $H_2O \cdot l^{-1} \cdot s^{-1}$) Values (Mean ± SD) for Each Anesthetic for Each Dose prior to Challenges

Concentration	Raw (cm $H_2O \cdot l^{-1} \cdot s^{-1}$)
Thiopental	
0	1.975 ± .82
5.6×10^{-5}	1.957 ± .91
1.9×10^{-4}	2.188 ± .93
5.6×10^{-4}	2.425 ± .99
Ketamine	
0	1.875 ± .55
5.4×10^{-5}	2.050 ± .71
1.8×10^{-4}	2.025 ± .62
5.4×10^{-4}	2.033 ± .60
Propofol	
0	2.000 ± .79
8.4×10^{-5}	2.013 ± .82
2.8×10^{-4}	2.175 ± .88
8.4×10^{-4}	2.083 ± .95

There was no significant change in prechallenge Raw with either thiopental ($P = 0.82$), ketamine ($P = 0.94$), or propofol ($P = 0.97$) at any of the concentrations administered.

Thiopental, at all of the doses administered, did not attenuate R_{aw} during either VNS or infusion of methacholine. At concentrations of 5.6×10^{-5} M, 1.9×10^{-4} M, and 5.6×10^{-4} M of thiopental, VNS increased R_{aw} to 94 ± 25%, 91 ± 17%, and 80 ± 28% of control stimulation, respectively ($P = 0.92$). Similarly, thiopental had no effect on the increase in R_{aw} with methacholine challenge. Airways resistance increased to 95 ± 12%, 88 ± 18%, and 195 ± 90%, respectively ($P = 0.14$).

Alternatively, propofol and ketamine had a profound effect on the airway responses to stimulation. Propofol caused a dose-dependent attenuation in the VNS-induced bronchoconstriction. At concentrations of 8.4×10^{-5} M, 2.8×10^{-4} M, and 8.4×10^{-4} M, VNS increased R_{aw} to only 83 ± 5%, 50 ± 5%, and 26 ± 11% of maximum (fig. 1, $P < 0.0001$). Further, propofol had an effect on methacholine-induced airway constriction but only at the highest concentration. At the concentrations administered, methacholine increased R_{aw} to 124 ± 19%, 96 ± 14%, and 43 ± 27% of maximum (fig. 2, $P = 0.05$).

Ketamine showed the greatest decrease in the airway response to VNS. At concentrations of 5.4×10^{-5} M,

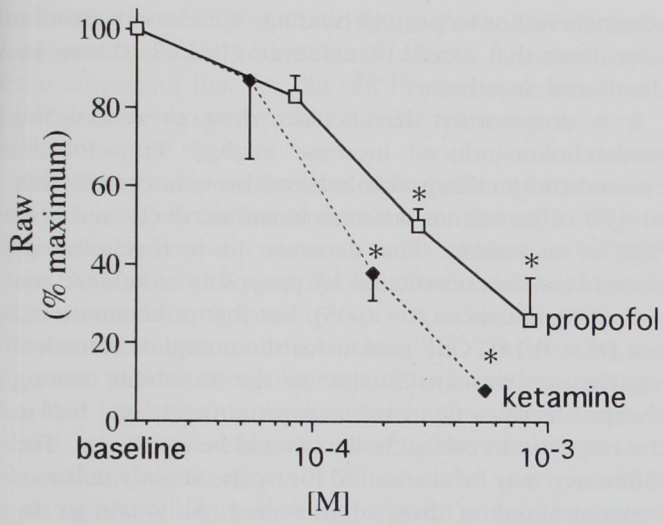

Fig. 1. Raw response to vagal nerve stimulation in eight sheep during increased doses of propofol (squares) and ketamine (diamonds). *$P < 0.05$ compared with baseline.

1.8×10^{-4} M, and 5.4×10^{-4} M, VNS increased R_{aw} to only 87 ± 19%, 38 ± 7%, and 8 ± 2%, respectively (fig. 1, $P = 0.0004$). At the concentrations delivered, methacholine increased R_{aw} to 114 ± 14%, 108 ± 17%, and 56 ± 17% of maximum (fig. 2, $P = 0.14$).

For the VNS challenge, the mean ED_{50} values for ketamine and propofol were $1.52 \pm 0.58 \times 10^{-4}$ and $3.54 \pm 0.63 \times 10^{-4}$, respectively. The ED_{50} value for ketamine was significantly lower than the ED_{50} value for propofol during VNS ($P = 0.03$). For the methacholine challenge, the ED_{50} values for ketamine and propofol were $7.93 \pm 3.3 \times 10^{-4}$ and $5.30 \pm 0.88 \times 10^{-4}$, respectively, which were not significantly different ($P = 0.38$).

Discussion

Our results show that propofol and ketamine protect against induced airway constriction compared with thiopental. Further, the major mechanism of this bronchoprotection was attenuation of neurally mediated constriction with minimal effects through attenuation of direct airway smooth muscle contraction.

Because the animals needed to be anesthetized during the study, we used a continuous infusion of pentobarbital to maintain anesthesia. We chose pentobarbital because it should not have significant effects on airway reactivity at maintenance doses.[31] In addition, a 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 our results. Further, beyond an adequate depth of anesthesia, deepening barbiturate anesthesia does not appear to influence airway reactivity or tone.[32,33] The finding that the infusion of thiobarbiturate in combination with the pentobarbital intravenous anesthetic agent had no effect on either VNS or methacholine-induced airway constriction also supports the lack of effect of the maintenance pentobarbital anesthesia.

We chose concentrations of drug that would be clinically relevant. In a recent study, Ludbrook *et al.*[34] examined the rate of administration of propofol on peak arterial concentrations of propofol. When 100 mg of propofol was administered at 200 mg/min, a peak brain arterial concentration of 30 μg/ml was measured, which would correspond to a concentration of 1.7×10^{-4} M, and in the middle of our dose range. Therefore, the doses we used appear to be clinically relevant as measured by doses for induction of anesthesia in sheep.

One of our goals was to study the direct bronchoprotective effects of these anesthetic agents and to eliminate any potential confounding effects that these agents might induce through circulating catecholamines systemically. We continuously measured the blood pressure and heart rate in each animal throughout the study. Because the heart rate was profoundly affected by the VNS challenges, we did not analyze this variable as a measure of systemic catecholamine release. In addition, we believed that any increase in systemic catecholamines from the administration of ketamine would

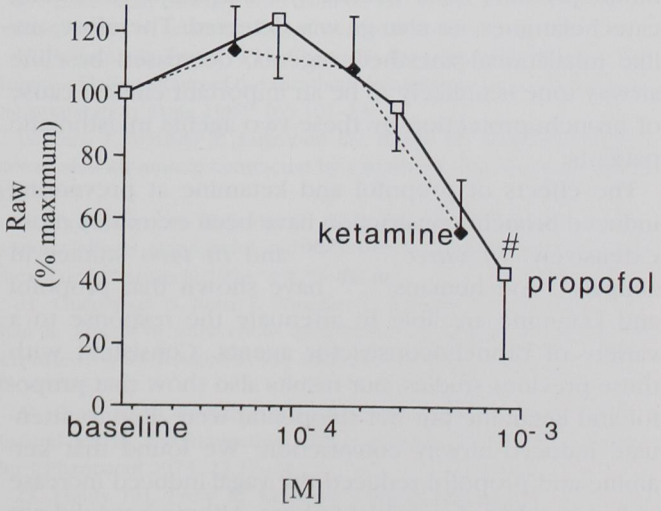

Fig. 2. Raw response to methacholine in eight sheep during increased doses of propofol (squares) and ketamine (diamonds). #$P < 0.05$ compared with baseline.

be detected easily by increased blood pressure, which we measured continuously by an indwelling arterial catheter. We found no significant changes in blood pressure during the infusion of ketamine nor the other two anesthetic agents into the bronchial artery, even at the highest concentrations. This supports our belief of a lack of significant systemic delivery of the anesthetic agents that were infused into the bronchial artery. Therefore, the decrease in airway responses we observed were local to the airways and not attributable to changes in circulating catecholamines or systemic changes.

Although the effects of inhalational anesthetic agents on baseline airway tone have been demonstrated clearly to cause relaxation,[8] the effects of intravenous agents such as propofol and ketamine are inconclusive. Several investigators have reported relaxant effects of ketamine and propofol on airway tone *in vitro,*[17,20] and others have reported no effect of these drugs on smooth muscle tone.[18,35] In an older clinical study reported by Huber *et al.,*[14] intravenously administered ketamine caused a dose-dependent decrease in R_{aw} in healthy subjects and in those with acute and chronic reactive airways disease. These patients were intubated, however, which would have increased R_{aw}. Further, prevention of reuptake of circulating catecholamines from the intravenous administration of ketamine[15] is the most likely explanation of the observed decrease in R_{aw} with increasing ketamine doses.[23,25] Our results do not support an effect of these drugs on baseline airway tone. We observed no decrease in baseline tone even at the highest concentration delivered directly to the airways. Further, using systemic blood pressure as a marker for increased circulating catecholamines, no change was detected. Therefore, unlike inhalational anesthetic agents, decreased baseline airway tone is unlikely to be an important clinical cause of bronchoprotection by these two agents in asthmatic patients.

The effects of propofol and ketamine at preventing induced bronchoconstriction have been examined more extensively. *In vitro*[16–21,35,36] and *in vivo* studies in animals[37] and humans[38–40] have shown that propofol and ketamine are able to attenuate the response to a variety of bronchoconstrictor agents. Consistent with these previous studies, our results also show that propofol and ketamine but not thiopental were able to attenuate induced airway constriction. We found that ketamine and propofol reduced the vagal-induced increase in R_{aw} in a dose-dependent fashion. Although we did not observe complete prevention of the vagal-induced increase in R_{aw}, this may be attributable to the doses administered or to protein binding. We chose to administer doses that would be achieved clinically during induction of anesthesia.[41–43]

It is noteworthy that neither drug prevented the methacholine-induced increase in R_{aw}. Propofol decreased the methacholine-induced bronchoconstriction to 43% of maximum whereas ketamine decreased it to 56% of maximum. The decrease in methacholine-induced bronchoconstriction by propofol did achieve statistical significance ($P = 0.05$), but that of ketamine did not ($P = 0.14$). One reason for this marginal statistical significance was attributable to the variability among sheep. Clearly, a decrease to approximately one half in the response to methacholine should be significant. The difference may be accounted for by the slightly different concentrations of drug administered. Although we infused the ketamine and propofol at the same rate, the difference in molecular weight led to a slightly higher molar concentration of propofol to be administered compared with ketamine. Whether reaching statistical significance at the highest dose we infused or at higher doses has clinical relevance remains in doubt, however. It is clear that at the lower doses we administered that are clinically relevant, the major effect of these drugs was on neural responses.

Consistent with our findings, several investigators have examined the mechanisms for neural depression by ketamine and propofol. Shrivastav[26] showed that ketamine, applied externally to giant squid axon, depolarized the nerve in a concentration-dependent fashion, reduced inward peak transient currents, and reduced steady-state current. Cronnelly *et al.*[22] demonstrated that ketamine affected the amplitude but not the frequency of miniature end-plate potentials of frog sartorius muscle.

Further, McGrath *et al.*[24] showed that ketamine depressed preganglionic sympathetic discharge in a dose-related fashion in rabbits. The results from Lundy and Frew[23] and Nedergaard[25] suggested that ketamine affected neural transmission by blocking extraneuronal uptake of catecholamines through inhibition of a neuronal membrane pump, which transports norepinephrine into the adrenergic neurones. Biddle *et al.*[44] examined 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. Any direct effect of the drugs on smooth muscle, however, would also inhibit a neurally mediated bronchoconstriction. Our findings are consis-

tent with the ability of these drugs to diminish neural responses through prejunctional effects. It was somewhat surprising that we did not observe a decrease in baseline tone; however, this may be related to the resting tone in the sheep.

That the primary mechanism of propofol and ketamine inhibition of bronchoconstriction is through neural mechanisms is also consistent with clinical investigations. Ketamine and propofol have been shown to protect against bronchoconstriction on induction of anesthesia and intubation of the trachea.[10–12] The increase in R_{aw} with airway manipulation such as bronchoscopy or tracheal intubation is mediated through neural mechanisms, which can also be blocked by the administration of local anesthetic agents.[45] Whether the exact mechanism of neural depression by propofol and ketamine is the same as that of local anesthetic agents remains to be determined.

Finally, whether propofol and ketamine are effective at reversing bronchoconstriction is currently not clear. There is some anecdotal evidence that propofol[40,46] and ketamine[13] can reverse bronchoconstriction. When bronchoconstriction was induced in healthy subjects with ultrasonic aerosols, however, inhaled halothane but not intravenously administered ketamine reversed the increased R_{aw}.[47] Unfortunately, our study was not designed to address this question.

Propofol and ketamine attenuate induced bronchoconstriction. Both have local effects on the airways, with their major mechanism of bronchoprotection occurring through depression of neurally induced bronchoconstriction. In addition, these drugs depress direct airway smooth muscle activation, but this appears to be less important at clinically relevant concentrations. Furthermore, ketamine is more potent than propofol at preventing neurally induced bronchoconstriction.

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