Laboratory Investigations

Differential effects of propofol, thiamylal and ketamine on the cricothyroid and posterior cricoarytenoid muscles of the canine larynx

Hiroshi Iwasaki MD PhD, Hideya Ohmori MD,
Masanori Yamauchi MD, Akiyoshi Namiki MD PhD

Purpose: To measure the electromyographic (EMG) responses of the phasic discharge in the cricothyroid (CT; a tensor muscle of the vocal folds) and the posterior cricoarytenoid (PCA; sole abductor muscle of the vocal folds) following intravenous infusion of propofol $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, thiamylal $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, or ketamine $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for five minutes.

Design: Prospective, nonrandomized, controlled animal study.

Setting: University research laboratory.

Subjects: Fifteen mongrel dogs, including three groups of five animals in each group.

Interventions: Under 0.2–0.3% halothane and oxygen anesthesia with spontaneous ventilation, phasic EMG activities of the CT and PCA muscles were recorded in an identical manner after the administration of each drug.

Measurements and main results: Propofol infusion produced almost equal suppression of EMG activity of the CT and the

PCA with time and three minutes after the start of infusion of propofol there was a significant depression of the phasic activities in the both muscles; EMG activity of the CT and the PCA was 33.8 ± 21.2 and $36.6 \pm 22.9\%$ (% of control, mean $\pm$ SD) respectively ($P < 0.05$). Thiamylal selectively reduced rhythmic discharges in the CT muscle during spontaneous breathing and significant depression of discharge in the CT muscle was observed three minutes after the drug ($47.3 \pm 24.9\%$, $P < 0.05$). In contrast, both phasic EMG activities of the CT and the PCA were rhythmically active and the differential sensitivity between the CT and the PCA muscles was not observed after ketamine, even after ten minutes of administration.

Conclusions: This study confirms a difference in sensitivity between the CT and the PCA muscles, demonstrating that the intrinsic laryngeal muscles do not behave similarly after the administration of conventional intravenous anaesthetic agents.

Key words

ANAESTHETICS, INTRAVENOUS: propofol, thiamylal, ketamine;

LARYNX: anatomy, vocal cords.

From the Department of Anesthesiology, Sapporo Medical University, School of Medicine, Sapporo, Japan 060.

Address correspondence to: Dr. H. Iwasaki, Department of Anesthesiology, Sapporo Medical University, School of Medicine, South-1, West-16, Chuoku, Sapporo, Japan 060.

Accepted for publication 31st August, 1995.

Objectif: Mesurer la réponse électromyographique (EMG) de la décharge phasique du muscle cricothyroïdien (CT: un des muscles tenseurs des cordes vocales) et la cricoaryténoïdien postérieur (CAP: le seul muscle abducteur des cordes vocales) après une perfusion intraveineuse de propofol $1,0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, de thiamylal $1,0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ou de kétamine $0,5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ pendant cinq minutes.

Organisation de l'étude: Prospective, non aléatoire, contrôlée, sur des animaux.

Milieu: Laboratoire de recherche universitaire.

Sujets: Quinze chiens de race commune divisés en trois groupes de cinq.

Interventions: Sous anesthésie en ventilation spontanée à

l'halothane 0,2–0,3% en oxygène, l'activité phasique EMG des muscles CT et CAP est enregistrée de manière identique après l'administration de chaque agent.

Mesures et principaux résultats: La perfusion de propofol produit une suppression presque identique de l'activité EMG du CT et CAP avec le temps. Trois minutes après le début de la perfusion de propofol, on constate une dépression importante de l'activité phasique des deux muscles; l'activité phasique du CT et du CAP est respectivement de $33,8 \pm 21,2$ et $36,6 \pm 22,9$ (% du contrôle, moyenne $\pm$ ET, $P < 0,05$). Par contre, l'activité EMG phasique du CT et du CAP était en harmonie et une différence de sensibilité entre les muscles CT et CAP n'a pas été observée avec la kétamine, même après dix minutes d'administration.

Conclusion: Cette étude confirme la différence de sensibilité qui existe entre les muscles CT et CAP et démontre que les muscles intrinsèques du larynx ne se comportent pas de la même façon après l'administration des anesthésiques intraveineux usuels.

Recently, the activities of the intrinsic laryngeal muscles have received much attention in anaesthesia practice, since they play an important role in the maintenance and protection of the airway. Various forms of anaesthesia are known to alter the activity of the intrinsic laryngeal muscles.^{1,2} It would be useful to evaluate the effects of intravenous anaesthetic agents on the different laryngeal muscles of the vocal cords separately, as vocal cord position is determined by the concurrent activity of the intrinsic laryngeal muscles. However, there is little information about the actions of conventional intravenous anaesthetics, especially the newly developed intravenous anaesthetic agent propofol on the intrinsic laryngeal muscles.

The purpose of this study was to compare the activities of the cricothyroid (CT; a tensor muscle of the vocal folds) and the posterior cricoarytenoid (PCA; sole abductor muscle of the vocal folds) muscles following propofol, thiamylal and ketamine administration in dogs.

Methods

After approval by our Animal Care and Use Committee, we studied 15 mongrel dogs of both sexes with a mean body weight of 11.5 kg (range 11–14 kg). Animals were anaesthetized with $10 \text{ mg} \cdot \text{kg}^{-1}$ of a mixed solution of α -chloralose ($45 \text{ mg} \cdot \text{mL}^{-1}$) and urethane ($450 \text{ mg} \cdot \text{mL}^{-1}$) *iv* and anaesthesia was maintained with halothane (end-tidal concentration of 0.2–0.3%) in oxygen, and supplemental doses of the α -chloralose and urethane solution were used during the operative procedure. Body temperature was maintained between 37–38°C using an infrared lamp. The neck was opened in the mid-line, and

the larynx was exposed carefully, avoiding injury to nerves and vessels. A tracheotomy was performed low in the neck with a T-shaped cannula, the stem being inserted toward the lung. The short arm of the T was connected to a gas stream from a reservoir to allow inhalation of anaesthetic gas and oxygen. Care was taken to adjust the flow to avoid disturbance of spontaneous respiration.

The electromyographic (EMG) recording electrodes consisted of fine insulated stainless steel wires exposed at the tip for 0.5 mm. Each wire was coiled around the barrel of a 22-ga needle, and the bare tip was bent back along the inside of the barrel. The needle (carrying the electrodes) was inserted into the CT and the PCA muscles and then withdrawn, leaving the hooked-wire electrodes embedded in the CT and PCA muscles. Access to the PCA muscle was obtained by pulling the larynx up and to the side, taking care not to damage the recurrent nerve and to preserve the inferior laryngeal blood vessels. When the electrodes were inserted correctly into the laryngeal muscles, the CT showed phasic EMG activity during expiration, while the PCA did so during inspiration.

After surgery and a 30 min equilibration period, baseline EMG recordings of both muscles had been obtained with the animals breathing light halothane and oxygen for at least five minutes. Animals were randomly assigned to one of the three treatment groups ($n = 5$ in each group) and were infused with propofol $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, thiamylal $1.0 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, or ketamine $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for five minutes. Animals breathed spontaneously throughout the study. The raw EMG activities in the CT and PCA muscles were amplified, filtered (100–2000 Hz), and integrated to give a moving time average with a time constant of 100 msec (Neuromatic 2000, Dantec, Copenhagen, Denmark). The amplitudes of expiratory activity in the CT and inspiratory activity in the PCA were determined by the peak height of the integrated EMG above electrical zero. The EMG activities after the administration of intravenous anaesthetic agents were expressed as a percentage of the maximum peak activities in each subject. The average values of each variable were determined for at least five consecutive respiratory cycles.

Data were expressed with the standard deviation of the mean. All comparisons were analyzed with two-way, repeated measures analysis of variance (ANOVA) followed by *post hoc* testing with Scheffe's F test. $P < 0.05$ was considered significant.

Results

There were no differences in the peak heights of baseline EMG activities for each muscle along the three

FIGURE 1 Representative recordings of compound and integrated EMG activities of the cricothyroid (CT) and posterior cricoarytenoid (PCA) muscles after propofol 1.0 mg · kg⁻¹ · min⁻¹.

FIGURE 2 The peak heights of cricothyroid (CT) and posterior cricoarytenoid (PCA) activities as a percentage of their control values after intravenous administration of propofol 1.0 mg · kg⁻¹ · min⁻¹. All data represent mean ± SD.

groups of animals. The laryngeal muscles during spontaneous breathing exhibited a characteristic pattern of discharge throughout the study; simultaneous recordings of the EMG activities in the laryngeal muscles showed phasic discharges in the PCA occurring with inspiration and alternating with activity in the CT during expiration in all subjects.

Characteristic EMG traces from the CT and PCA muscles following intravenous infusion of propofol 1.0 mg · kg⁻¹ · min⁻¹ are shown in Figure 1. Rhythmic activities in both the CTA and PCA muscles decreased progressively and reached 1.3 ± 2.5% and 7.1 ± 11.2% (mean ± SD) of their control (pre-drug activity) values, respectively, five minutes after the administration of propofol (Figure 2). On the other hand, after thiamylal infusion, the CT exhibited a progressive decrease in

FIGURE 3 The peak heights of cricothyroid (CT) and posterior cricoarytenoid (PCA) activities as a percentage of their control values after intravenous administration of thiamylal 1.0 mg · kg⁻¹ · min⁻¹. All data represent mean ± SD. *P < 0.05 versus the PCA muscle.

FIGURE 4 The peak heights of cricothyroid (CT) and posterior cricoarytenoid (PCA) activities as a percentage of their control values after intravenous administration of ketamine 0.5 mg · kg⁻¹ · min⁻¹. All data represent mean ± SD.

activity with time, although phasic inspiratory activity of the PCA remained at about the same level. The peak heights of phasic CT activity decreased three minutes after thiamylal ($P < 0.05$) and reached to 26.4 ± 12.1% of its control value five minutes after the drug ($P < 0.01$), while there was no decrease in the PCA activity following thiamylal (Figure 3). In contrast, no decrease in rhythmic EMG activities in either muscle was demonstrated in any of the five animals with ketamine (Figure 4), even after ten minutes of administration.

Discussion

In this study we have demonstrated that intravenous anaesthetic agents used in anaesthesia produce differential patterns of depression in the intrinsic laryngeal muscle. While propofol reduced the phasic activity of both muscles, ketamine reduced neither and thiamylal reduced only the activity of the CT.

Normal pharyngolaryngeal reflexes contribute to prevent the risk of silent aspiration during anaesthesia. Several investigators have shown that the laryngeal closure-reflex is depressed during various forms of conventional anaesthesia.^{3,4} When the depth of barbiturate anaesthesia is increased, the spontaneous EMG in the laryngeal adductor muscles including the CT muscle disappears well in advance of that in the abductor muscle.^{5,6} Thus, phasic expiratory activity is profoundly influenced by barbiturate anaesthesia, as observed in the present study.

Sherry and Megirian reported that ketamine injection did not abolish periodic, on-going adductor and abductor laryngeal muscle activity.⁶ The relative preservation of laryngeal-closure reflexes during induction of anaesthesia with ketamine has been reported in clinical practice.^{7,8} With increasingly deeper levels of ketamine anaesthesia, both the CT and PCA muscles remained rhythmically active, and a differential sensitivity between the adductors and abductor was not observed in the present study. These results suggest a relative over-activity of the laryngeal reflexes during ketamine anaesthesia.

On the other hand, it has been observed clinically that propofol decreases the tone of the muscles of the jaw and reduces the pharyngeal reflexes more than do barbiturates.^{9,10} The almost equal suppression of the EMG activities in the CT and PCA muscles presently observed after propofol infusion may contribute to the great suppression of laryngeal reflexes during induction of anaesthesia with propofol.

In the present study, a continuous infusion was chosen for the administration of intravenous anaesthetics. This has several advantages for observing differential sensitivity between the two laryngeal muscles over a single injection. Firstly, to compare the differential effects of intravenous anaesthetics on the two muscles, it is desirable to use equivalent doses of the drugs. However, the relative potencies of intravenous anaesthetics have been expressed in a variety of terms by different workers.^{11,12} This method makes it possible to evaluate the effects of the drugs in a wide range, including clinical doses in the induction of anaesthesia, on the laryngeal muscles. In addition, when no change of rhythmic activity of the two laryngeal muscles after the drug is observed, it is possible to observe the responses

of the muscles for a long time. In this study, phasic activity in the CT and PCA muscles following ketamine infusion was observed for ten minutes in all subjects. Secondly, this technique produces respiratory depression more slowly than administration by a single injection.

We did not investigate either the precise site of action or the mechanisms of anaesthetic agents in these muscles. However, it is clear from our results that different patterns of changes in the glottic resistance and diameter may occur in anaesthesia with intravenous agents. It can be inferred that the relative preservation of CT muscle activity may enable the valve-like larynx to continue to maintain its function, thus ensuring the laryngeal closure reflex after ketamine administration. The PCA muscle is the sole abductor of the vocal folds; it abducts the arytenoid cartilages and widens the glottis. A progressive increase in glottic diameter is observed with increasing PCA muscle activity. The CT muscle is a tensor but not a powerful adductor of the larynx. Physiological levels of CT activity have no effect on laryngeal resistance or glottic diameter. Laryngeal resistance is increased when the CT muscle is stimulated supramaximally.¹³ The mechanical role of the CT muscle in the larynx is not simple, although the primary function of this muscle is to increase tension in the vocal cords. In the present study, the CT was selected to evaluate the EMG activity as an adductor laryngeal muscle following intravenous anaesthetic agents because it is easily accessible. To insert the electrodes into another laryngeal adductor muscle such as the lateral cricoarytenoid muscle it is necessary to resect the surrounding connective tissues of the larynx. In addition, it is known that the adductor laryngeal muscles, including the CT muscle, behave similarly with anaesthesia and changes in respiratory loads.^{5,14}

Several studies have documented that phasic activities of the CT and PCA muscles responded to respiratory stimuli such as hyperventilation, hypercapnia, and upper airway load.^{15,16} This might have caused the changes in the two muscles observed in the present study. In a clinical practice, however, intravenous anaesthetics could interact with the spontaneous changes in the respiratory conditions.

It is concluded that there are quite distinct differential patterns of suppression of phasic EMG activity between the CT and the PCA muscles following propofol, thiamylal and ketamine infusion. The position of the vocal cords is the overall result of the concurrent activity of a number of muscles including the cervical strap muscles. To understand the laryngeal reflex and intubating conditions further studies must address anaesthetics' activity in the key cervical strap muscles as well as the other

intrinsic laryngeal muscles affecting the action of the vocal cords.

Acknowledgement

We thank Mr. Toshihiko Katayama, laboratory technologist.

References

- 1 Nishino T, Yonezawa T, Honda Y. Differential laryngeal responses during respiratory arrest produced by hypoxia withdrawal, thiopentone, ketamine, and lidocaine in cats. *Anesthesiology* 1982; 56: 280–5.
- 2 Megirian D, Sherrey JH. Respiratory functions of the laryngeal muscles during sleep. *Sleep* 1980; 3: 289–98.
- 3 Nakamura F, Uyeda Y, Sonoda Y. Electromyographic study on respiratory movements of the intrinsic laryngeal muscles. *Laryngoscope* 1958; 68: 109–19.
- 4 Rattenborg CC, Barton MD, Kain ML, Logan WJ, Konrad HR, Holaday DA. Reflex activity of the larynx during breathing. *Anesthesiology* 1963; 24: 139–40.
- 5 Brewer DW, Dana ST. Investigations in laryngeal physiology: the canine larynx. Part 2. *Ann Otol Rhinol Laryngol* 1963; 72: 1060–75.
- 6 Sherrey JH, Megirian D. Spontaneous and reflexly evoked laryngeal abductor and adductor muscle activity of cat. *Exp Neurol* 1974; 43: 487–98.
- 7 Corssen G, Miyasaka M, Domino EF. Changing concepts in pain control during surgery: dissociative anesthesia with CI-581. A progress report. *Anesth Analg* 1968; 47: 746–59.
- 8 Yeung ML, Lin RSH. Laryngeal reflexes in children under ketamine anaesthesia. *Br J Anaesth* 1972; 44: 1089–92.
- 9 Mackenzie N, Grant IS. Comparison of the new emulsion formation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *Br J Anaesth* 1985; 57: 725–31.
- 10 De Grood PMRM, Van Egmond J, Van de Wetering M, Van Beem HB, Booij LHDJ, Crul JF. Lack of effects of emulsified propofol ('Diprivan') on vecuronium pharmacodynamics – preliminary results in man. *Postgrad Med J* 1985; 61 (Suppl.3): 28–30.
- 11 Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *Eur J Anaesthesiol* 1986; 3: 11–7.
- 12 McKeating K, Bali IM, Dundee JW. The effects of thiopentone and propofol on upper airway integrity. *Anaesthesia* 1988; 43: 638–40.
- 13 Konrad HR, Rattenborg CC. Combined action of laryngeal muscles. *Acta Otolaryngol (Stockh)* 1969; 67: 646–9.
- 14 Green JH, Neil E. The respiratory function of the laryngeal muscles. *J Physiol* 1955; 129: 134–41.
- 15 Tully A, Brancatisano A, Loring SH, Engel LA. Influence of posterior cricoarytenoid muscle activity on pressure-flow relationship of the larynx. *J Appl Physiol* 1991; 70: 2252–8.
- 16 Wheatley JR, Brancatisano A, Engel LA. Cricothyroid muscle responses to increased chemical drive in awake normal humans: *J Appl Physiol* 1991; 70: 2233–41.