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# *Priming Doses of Atracurium and Vecuronium Depress Swallowing in Humans*

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**The administration of low doses of muscle relaxant may cause peripheral muscular weakness including difficulty in swallowing. In the present study, the effect of priming doses of atracurium and vecuronium on swallowing was studied. Sixty patients undergoing elective surgery under general anesthesia were divided randomly into four groups of 15 patients and received as a priming dose either vecuronium (10 or 15 μg/kg) or atracurium (50 or 75 μg/kg). Swallowing muscle activity was measured by electromyography using submental surface electrodes. Swallowing was initiated by administration of 0.3 ml distilled water through an oral catheter. Swallowing reflex was determined by measuring the latency time (*i.e.*, time from water administration to start of EMG activity of glossal muscles). Swallowing activity was determined by integration of the EMG of glossal muscles during swallowing. Peripheral muscle strength was determined by hand grip strength. Swallowing reflex activity and peripheral muscle strength were measured before and 3 and 6 min after administration of vecuronium or atracurium. Latency time remained unchanged after any of the priming doses. Integrated EMG decreased significantly ($P < .001$) 3 and 6 min after all priming doses tested (42–75% of baseline value). Only after atracurium 75 μg/kg was the hand grip strength significantly decreased ($P < .01$). These results suggest that owing to its effect on swallowing, the priming dose should be used with caution. (Key words: Airway. Neuromuscular relaxants: atracurium, vecuronium.)**

THE ONSET OF the neuromuscular blocking effect of nondepolarizing neuromuscular blocking agents (NMBA) is slow.[1] This phenomena is explained by the buffering effect of the neuromuscular junction, which slows the rate of increase in the concentration of NMBA in the synaptic cleft.[2] To decrease the onset of action of NMBA, it has been proposed that a small subparalyzing dose of NMBA, sufficient to occupy a significant fraction of post junctional acetylcholine receptors but insufficient to cause muscular weakness be administered prior to a larger paralyzing dose.[3] Several protocols have demonstrated the effectiveness of a priming dose in decreasing the onset time of NMBA,[4,5] and this technique has gained some clinical popularity. However the safety and efficacy of this technique is limited: too small a priming dose may not hasten the onset time and too large a dose may cause significant muscular weakness, such as diplopia,[6] difficulty in swallowing,[6] and difficulty in breathing.[6,7] Of greater importance, aspiration pneumonia has been reported following the use of the priming dose.[8] Recently it was shown that 20 μg/kg pancuronium impaired swallowing in human volunteers.[9] This dose, which is higher than the pancuronium dose recommended for priming,[5] also caused significant peripheral muscular weakness.[9] In the present study, we evaluated the effect of priming doses corresponding to 10% and 15% of the full intubating dose of 0.5 mg/kg atracurium and 0.1 mg/kg vecuronium, respectively, on swallowing in patients undergoing elective surgery under general anesthesia.

## Materials and Methods

### PATIENTS

Sixty surgical patients, ASA physical status 1 or 2, 47 ± 15 yr of age (mean ± SD), were studied after informed consent was given. Patients were scheduled to have general anesthesia with tracheal intubation for their surgery. No premedication was given either the evening or the morning before.

### PROTOCOL

Patients were breathing 100% oxygen for 3 min before the administration of the NMBA and were monitored with finger pulse oximetry ($SpO_2$; model N-200, Nellcor®, Jouy en Josas, France) throughout the study. Peripheral oxygen desaturation was defined as $SpO_2$ less than 92% for 20 s. All patients were randomly divided into four groups of 15 patients. Groups $Vec_{10}$ and $Vec_{15}$ received 10 and 15 μg/kg vecuronium, respectively, and groups $Atr_{50}$ and $Atr_{75}$, 50 and 75 μg/kg atracurium, respectively. Each set of measurements was performed before and 3 and 6 min after the dose of muscle relaxant. Thereafter, the patients were anesthetized with thiopental and fentanyl and the full intubating dose of either atracurium or vecuronium was given.

### METHODS

All patients were studied while supine. Swallowing was initiated by rapid bolus of 0.3 ml distilled water admin-

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istered through an orally placed 15-mm ID catheter using a hypodermic syringe. The tip of the catheter was 5 cm behind the incisors and the catheter was fixed with adhesive tape on the lower lip. Because there is an interrelationship between swallowing and breathing,[10] breathing was monitored by indirect spirometry (Respitrace®, Sebac, Pantin, France) and the signal displayed on an oscilloscope. Water administration through the oral catheter was performed at the end of expiration. The swallowing reflex was measured according to the technique of Nishino *et al.*[11] Surface electrodes (electrodes 13K60 Dantec®, Les Ullis, France) were used to register the electromyographic activity (EMG). A pair of submental electrodes were placed, each 1 cm from the midline and 1.5 cm above the hyoid bone. EMG during swallowing was amplified and band pass filtered from 30 to 300 Hz and then rectified and integrated (EMGi) with a time constant of 100 ms. The area of the integrated signals were measured digitally. EMG, EMGi, and respiratory movements from Respitrace® bands were simultaneously recorded (TA 2000 recorder Gould electronics®, Longjumeau, France). A pressure transducer was connected to the outside of the syringe used for water injection to detect the time of injection by simultaneous registration of the increase in pressure during injection. The latency time of the swallowing reflex consisted of the time elapsing between injection and the beginning of the EMG. The results from each set of three measurements over 1 min were averaged. The maximum grip strength was measured using a dynamometer (Digital pinch/grip analyser 375®, Medical Research Ltd., Leeds, England) in the hand of the arm without the intravenous infusion.

### Statistical Analysis

All values are expressed as mean ± SD. Comparisons among each group were performed using a two-way analysis of variance and paired Student's *t* test. Comparisons between groups Atr 50 and Vec 10 and groups Atr 75 and Vec 15 were performed using unpaired Student's *t* test. A $P$ value $< .05$ was considered to be statistically significant.

TABLE 1. Demographic Characteristics

| | Atracurium | | Vecuronium | |
|---|---|---|---|---|
| | 50 μg·kg⁻¹ (n = 15) | 75 μg·kg⁻¹ (n = 15) | 10 μg·kg⁻¹ (n = 15) | 15 μg·kg⁻¹ (n = 15) |
| Age (yr) | 44 ± 9 | 50 ± 14 | 52 ± 18 | 44 ± 15 |
| Weight (kg) | 66 ± 10 | 66 ± 8 | 74 ± 7 | 72 ± 19 |
| Gender (M/F) | 8/7 | 6/9 | 11/4 | 7/8 |

Values are mean ± SD.

TABLE 2. Latency Time(s) of the Swallowing Reflex Measured before and 3 and 6 Min after the Priming Dose of Atracurium or Vecuronium

| | Atracurium | | Vecuronium | |
|---|---|---|---|---|
| | 50 μg·kg⁻¹ | 75 μg·kg⁻¹ | 10 μg·kg⁻¹ | 15 μg·kg⁻¹ |
| Before | 1.2 ± 0.3 | 1.2 ± 0.5 | 1.7 ± 0.5 | 1.5 ± 0.2 |
| 3 min | 1.2 ± 0.2 | 1.5 ± 0.5 | 1.6 ± 0.5 | 1.5 ± 0.3 |
| 6 min | 1.3 ± 0.3 | 1.4 ± 0.4 | 1.7 ± 0.4 | 1.5 ± 0.4 |

Values are mean ± SD.

## Results

The four groups were comparable in terms of age, weight, and gender distribution (table 1). None of the patients experienced an episode of hemoglobin oxygen desaturation during the study. After the administration of the priming dose of NMBA, the latency time was not changed in the four groups (table 2). The EMGi was significantly diminished in the four groups 3 and 6 min after the administration of NMBA (table 3). Atracurium (75 μg/kg) caused a significantly ($P < .05$) greater decrease in EMGi than vecuronium (15 μg/kg) at 3 and 6 min, respectively. No patients complained of serious respiratory discomfort at 3 and 6 min in groups $Atr_{50}$ and $Vec_{10}$. However two patients in group $Atr_{75}$ and one in group $Vec_{15}$ experienced respiratory discomfort, and anesthesia was induced before the end of the study. Peripheral voluntary muscle strength remained unaffected after the priming dose in the $Atr_{50}$, $Vec_{10}$, and $Vec_{15}$ groups, however in the $Atr_{75}$ group, it was significantly decreased ($P < .01$) at 3 and 6 min to 72% and 50% of baseline strength, respectively (table 4).

## Discussion

The principal findings of the present study are that: 1) the submental EMGi was constantly diminished during swallowing by all of the priming doses of atracurium or vecuronium; 2) in comparison to glossal muscles, the hand grip strength was only diminished after the largest dose of 75 μg/kg atracurium; and 3) the latency time of swallowing remained unaffected by any of the subparalyzing doses of vecuronium or atracurium. We choose to measure EMGi at 3 and 6 min after the dose of priming because these intervals have been advocated by Schwarz *et al.*[4] and Mehta *et al.*,[5] respectively, as the optimum delay before which the full paralyzing dose should be given.

By recording the submental integrated EMG, the activities of mylohyoid, geniohyoid, genioglossus, and anterior belly of digastric muscles are summated.[9,12] This measure of muscle function by electromyography does not allow a direct measure of the strength of glossal mus-

TABLE 3. Integrated Electromyographic Activity of Glossal Muscles during Swallowing 3 and 6 min after Priming Doses of Atracurium or Vecuronium

| Patient Number | Atracurium 50 $\mu g \cdot kg^{-1}$ | | Atracurium 75 $\mu g \cdot kg^{-1}$ | | Vecuronium 10 $\mu g \cdot kg^{-1}$ | | Vecuronium 15 $\mu g \cdot kg^{-1}$ | |
|---|---|---|---|---|---|---|---|---|
| | 3 min | 6 min | 3 min | 6 min | 3 min | 6 min | 3 min | 6 min |
| 1 | 72 | 64 | 28 | 0* | 67 | 50 | 89 | 82 |
| 2 | 60 | 80 | 50 | 47 | 70 | 86 | 64 | 55 |
| 3 | 30 | 60 | 30 | 0* | 67 | 86 | 64 | 68 |
| 4 | 80 | 94 | 67 | 57 | 88 | 90 | 56 | 46 |
| 5 | 63 | 77 | 17 | 17 | 63 | 60 | 70 | 52 |
| 6 | 90 | 90 | 77 | 66 | 77 | 90 | 64 | 52 |
| 7 | 85 | 85 | 46 | 20 | 43 | 59 | 70 | 60 |
| 8 | 53 | 59 | 60 | 33 | 67 | 69 | 39 | 64 |
| 9 | 77 | 56 | 35 | 30 | 26 | 50 | 75 | 61 |
| 10 | 63 | 61 | 57 | 46 | 58 | 62 | 60 | 62 |
| 11 | 33 | 83 | 20 | 45 | 30 | 63 | 78 | 44 |
| 12 | 90 | 95 | 52 | 50 | 45 | 56 | 0† | 0† |
| 13 | 47 | 63 | 70 | 58 | 58 | 69 | 68 | 56 |
| 14 | 50 | 88 | 44 | 29 | 54 | 75 | 67 | 72 |
| 15 | 70 | 76 | 77 | 52 | 76 | 70 | 86 | 69 |
| Mean | 59‡ | 75‡ | 49‡§ | 42‡§ | 59‡ | 69‡ | 68‡ | 58‡ |
| SD | 16 | 14 | 20 | 15 | 17 | 14 | 12 | 12 |

Data are percent of initial activity.
* Patient tracheal intubated before 6 min because of respiratory difficulty and EMgi given the value of 0%.
† Patient tracheal intubated before 3 min because of respiratory difficulty and EMgi given the value of 0%.
‡ $P < .001$ *versus* control value.
§ $P < .05$ *versus* vecuronium 15 $\mu g \cdot kg^{-1}$ at 3 min.
§ $P < .05$ *versus* vecuronium 15 $\mu g \cdot kg^{-1}$ at 6 min.

cles but of the sum of the motor units activated during swallowing.[13] Although, the contraction of glossal muscles during swallowing is not isometric, one can assume that the decreased EMGi corresponds to decreased muscle strength. Therefore, the percent decrease in EMGi reflects the degree of depression of muscle strength. By comparing the degree of depression of the EMGi to that of hand-grip strength, we suggest that glossal muscles are more sensitive to atracurium and vecuronium than are hand muscles.

A more pronounced neuromuscular blocking effect was observed on both the thumb and glossal muscles after 75 $\mu g/kg$ atracurium than after 15 $\mu g/kg$ vecuronium. The potency ratio of 5 that was used in the present study to compare atracurium and vecuronium is similar to the $ED_{95}$ ratio measured in anesthetized patients, the $ED_{95}$ of atracurium and vecuronium being 200 and 40 $\mu g/kg$, respectively.[14] Therefore the present findings suggest that the dose responses of atracurium and vecuronium are probably not parallel, and that at low subparalyzing doses, the potency ratio between atracurium and vecuronium may be greater than 5.

TABLE 4. Hand Grip Strength after the Administration of Priming Doses of Atracurium or Vecuronium

| | Atracurium 50 $\mu g \cdot kg^{-1}$ | Vecuronium 15 $\mu g \cdot kg^{-1}$ | Vecuronium 10 $\mu g \cdot kg^{-1}$ | Atracurium 75 $\mu g \cdot kg^{-1}$ |
|---|---|---|---|---|
| 3 min | 96 ± 17 | 01 ± 9 | 104 ± 10 | 72 ± 23* 1 |
| 6 min | 96 ± 11 | 96 ± 8 | 98 ± 4 | 50 ± 17* |

Data are percent of control.
* $P < .01$ *versus* control.

Using a similar study protocol of swallowing, Isono *et al.*[9] also observed that 20 $\mu g/kg$ pancuronium caused a more pronounced effect on glossal muscles than on hand muscles. The study of Isono *et al.*[9] differs in two respects from our study: 1) the study of Isono *et al.* was undertaken in young healthy male volunteers, whereas our study was undertaken in patients, and 2) pancuronium was used by Isono *et al.* at a dose of 20 $\mu g/kg$, which is equivalent to 15 $\mu g/kg$ vecuronium. However this dose of pancuronium caused a significant decrease in the hand grip strength and a train-of-four fade of the elicited thumb response, whereas we did not observe detectable peripheral paralysis with an equipotent dose of vecuronium. Our results are also in agreement with those of Pavlin *et al.*,[15] who evaluated the effect of several doses of d-tubocurarine in healthy volunteers. They observed that muscles contributing to swallowing were more sensitive to d-tubocurarine than were inspiratory muscles.[15] At a given level of paralysis swallowing was abolished, whereas maximum inspiratory pressure was only partially diminished. From their data,[15] it is however difficult to extrapolate a comparison between peripheral muscles and muscles contributing to airway protection.

There is large interindividual variability in the response to muscle relaxants, and this phenomena has been well documented with d-tubocurarine.[16] In the present study, we observed a more profound paralysis in three patients older than 60 years, two had received 75 μg/kg atracurium and one, 15 μg/kg vecuronium. This finding has to be considered as a potential respiratory complication induced by the priming dose. In most patients, subparalyzing doses of atracurium and vecuronium will partially decrease the swallowing capacity, but in a few patients, there is a risk of complete abolition of swallowing function. The absence of change in latency response after small doses of NMBA suggests that partial paralysis of glossal muscles is not associated with impairment of neural pathway involved in this reflex.

The results of the present study may have several clinical implications. Glossal muscle dysfunction may affect upper airway by several mechanisms: 1) During swallowing, contraction of geniohyoid and genioglossus muscles causes an elevation of the hyoid bone and the larynx.[13] As suggested by Isono *et al.*,[9] impairment of laryngeal elevation during swallowing may predispose the patients to aspiration of pharyngeal contents. 2) Glossal muscle dysfunction may decrease upper airway patency. The geniohyoid muscle acts as an upper airway dilator during inspiration by displacing the hyoid bone anteriorly,[17] and its partial paralysis may cause an increase in upper airway resistance, especially in patients in the supine position.[18] The alterations presently observed during the priming technique also may be met during recovery from neuromuscular blockade. If glossal muscles are also more sensitive than hand muscles during offset of paralysis, then the information provided from the usual monitoring of the thumb may not indicate the presence of residual effect of NMBA on swallowing function.

In summary, our results demonstrate that atracurium and vecuronium at the recommended doses of priming cause a decrease in activity of glossal muscle during swallowing in humans. Normal pathways involved in the swallowing reflex are not affected by subparalyzing doses of atracurium and vecuronium. Owing to the risk of respiratory complications, we believe that the priming technique should be used with caution.

## References

1. Miller RD, Rupp SM, Fisher DM, Cronnely R, Fahey MR, Sohn YJ: Clinical pharmacology of vecuronium and atracurium. ANESTHESIOLOGY 61:444–453, 1984
2. Jones RM: The priming principle: How does it work and should we be using it? Br J Anaesth 63(1):1–3, 1989
3. Paton WDM, Waud DR: The margin of safety neuromuscular transmission. J Physiol (Lond) 191:59–90, 1967
4. Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes F: Rapid tracheal intubation with vecuronium: The priming principle. ANESTHESIOLOGY 62:388–391, 1985
5. Mehta MP, Choi W, Cergis SD, Sokoll MD, Adolphson A: Facilitation of rapid endotracheal intubations with divided doses of nondepolarizing neuromuscular blocking drugs. ANESTHESIOLOGY 62:392–395, 1985
6. Hansen PH, Jorgensen BC, Ording H, Viby-Mogensen J: Pretreatment with non-depolarizing muscle relaxants: The influence on neuromuscular transmission and pulmonary function. Acta Anaesthesiol Scand 24:419–422, 1980
7. Rao TLK, Jacobs HK: Pulmonary function following "pretreatment" dose of pancuronium in volunteers. Anesth Analg 59: 659–661, 1980
8. Musich J, Walts LF: Pulmonary aspiration after a priming dose of vecuronium. ANESTHESIOLOGY 64:517–519, 1986
9. Isono S, Ide T, Kochi T, Mizuguchi T, Nishino T: Effect of partial paralysis on the swallowing reflex in conscious humans. ANESTHESIOLOGY 75:980–984, 1991
10. Nishino T, Yonezawa T, Honda Y: Effects of swallowing on the pattern of continuous respiration in human adults. Am Rev Respir Dis 132:1219–1222, 1985
11. Nishino T, Takizawa K, Yokokawa N, Higara K: Depression of the swallowing reflex during sedation and/or relative analgesia produced by inhalation of 50% nitrous oxide in oxygen. ANESTHESIOLOGY 67:995–998, 1987
12. Dantas R, Kern MK, Massey BT, Doods WJ, Kahnilas PJ, Brasseur JG, Lang IM: Effect of swallowed bolus variables on oral and pharyngeal phases of swallowing. Am J Physiol 258:G675–G681, 1990
13. Miller AJ: Deglutition. Physiol Rev 61:129–184, 1982
14. Smith CE, Donati F, Bevan DR: Cumulative dose-response with infusion: a technique to determine neuromuscular blocking potency of atracurium and vecuronium. Clin Pharmacol Ther 44: 56–64, 1988
15. Pavlin EG, Holle RH, Schoene RB: Recovery of airway protection compared with ventilation in humans after paralysis with curare. ANESTHESIOLOGY 70:381–385, 1989
16. Katz RL: Neuromuscular effects of d-tubocurarine, edrophonium and neostigmine in man. ANESTHESIOLOGY 28:327–336, 1967
17. Wiegand DA, Latz B, Zwillich CW, Wiegand L: Geniohyoid muscle activity in normal men during wakefulness and sleep. J Appl Physiol 69:1262–1269, 1990
18. Gal TJ, Arora NS: Respiratory mechanics in supine subjects during progressive partial curarization. J Appl Physiol 52:57–63, 1982