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The Effect of Neuromuscular Blockade with Vecuronium on Hemodynamic Responses to Noxious Stimuli in the Rat

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The effect of neuromuscular blockade with vecuronium on the hemodynamic responses to a noxious stimulus was investigated in male Sprague-Dawley rats. The rats were anesthetized with either halothane (group 1, n = 10), or isoflurane (group 2, n = 10). The maximum values for heart rate and mean arterial pressure during the noxious stimulus (base-tail clamp) were measured, and the maximum *changes* in these values (maximum *minus* prestimulation) were calculated. The responses were measured at two different anesthetic concentrations (0.6 × MAC, 0.75 × MAC), before and after vecuronium 1.0 mg·kg^{-1} iv. It was found that neuromuscular blockade with vecuronium did not reduce any of the hemodynamic responses measured, at either anesthetic concentration, in either the halothane or the isoflurane group. However, increasing the anesthetic concentration from 0.6 × MAC to 0.75 × MAC produced statistically significant ($P < 0.01$) reductions in several of the responses measured. The inability of vecuronium to reduce hemodynamic responses to noxious stimuli in this study suggests that neuromuscular blockade does not alter anesthetic depth in the rat. A knowledge of this "absence of effect" may be important for investigators who need to induce muscle relaxation in laboratory animals prior to examining the effect of anesthetic agents on hemodynamic responses to noxious stimuli. The results also question the ability of neuromuscular blockade to reduce anesthetic requirement, and support the view that neuromuscular blockade does not contribute to the anesthetic state. (Key words: Anesthesia: depth. Blood pressure: drug effects. Heart, pulse rate: drug effects. Neuromuscular relaxants: vecuronium bromide. Noxious stimuli: blood pressure; heart rate.)

ALTHOUGH THE HEMODYNAMIC effects of the neuromuscular blocking drugs in current use have been well characterized in both humans and animals,[1,2] there have been no direct studies of the effect these agents have on hemodynamic responses to noxious stimuli. However, the attenuation of hemodynamic responses to noxious stimuli is one of the most important goals of modern anesthesia, and neuromuscular-blocking drugs are among the most widely used. It is possible that neuromuscular-blocking drugs do affect hemodynamic responses to noxious stimuli, because it has been shown that pancuronium reduces anesthetic requirement in humans.[3]

A knowledge of the effect of neuromuscular blockade on hemodynamic responses to noxious stimuli is important not only for clinical anesthesiologists, but also for investigators who are examining the effects of anesthetic agents on hemodynamic responses in animals. Laboratory animals may require muscle relaxation to allow endotracheal intubation or controlled ventilation. In this situation, it is necessary to know the contribution, if any, that neuromuscular blockade has on the attenuation of hemodynamic responses to noxious stimuli.

Of the neuromuscular blocking drugs in current use, vecuronium has the least direct hemodynamic effects,[2] and would appear to be the most suitable drug with which to examine the effects of neuromuscular blockade on hemodynamic responses. The aim of the present study was to determine whether complete neuromuscular blockade with vecuronium reduces heart rate (HR) and mean arterial pressure (MAP) responses to a standardized noxious stimulus in the anesthetized rat.

Materials and Methods

All experiments were approved by the Pennsylvania State University College of Medicine Animal Care Committee, and conformed with the "Guiding Principles in the Care and Use of Animals" of the American Physiological Society. Two groups of animals were studied.

GROUP 1 (HALOTHANE)

Male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA, weight = 405 ± 13 g, mean ± SEM, n = 10) were anesthetized with 2% halothane (vol/vol) in O_2 in a plexiglass induction chamber. After tracheostomy, controlled ventilation was instituted using a pressure cycled ventilator (Analytical Specialties SAR-2, St. Louis, MO) and a nonrebreathing circuit. Anesthesia was continued with an inspired halothane concentration of 1.5% in O_2. The carotid artery pressure was monitored using an intravascular catheter (PE-50 tubing) filled with heparinized saline, connected to a Gould P23ID transducer which was calibrated to a mercury column. Venous access

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was established by introducing a similar catheter system into a jugular vein. Rectal temperature was servo controlled at 37° C using a heating mattress. The end-tidal fractions (F_{ET}) of CO_2 and halothane (H) were measured by mass spectrometry (Perkin-Elmer 1100 MGA, Pomona, CA) using a respiratory waveform monitoring technique.[4] Ventilation was adjusted to maintain $F_{ET}CO_2$ at 5.0 ± 0.5% (mean ± range). Continuous recordings of aortic pressure and heart rate, and intermittent recordings of $F_{ET}CO_2$ and $F_{ET}H$ were made on a Gould 2800 recorder. HR was obtained electronically from the arterial blood pressure waveform (pressure processor model 13–4615–52, Gould Inc, Cleveland, OH). Neuromuscular blockade was monitored by observing the evoked twitch response to transcutaneous stimulation (50 mA, 200 μs square wave using clip electrodes) of the right common peroneal nerve (Digistim III, Neuro Technology Inc., Houston, TX).

After instrumentation, the $F_{ET}H$ was reduced to 0.65 ± 0.05% (mean ± range), which is approximately equal to 0.6 × MAC_H (MAC_H = 1.11%),[5] for 30 min. A noxious stimulus was then applied at the base of the tail for 60 s using a 20 cm rubber-shod tubing clamp (Pilling Instruments, Fort Washington, PA, model 35-1375), clamped to the second ratchet. The absolute maximum MAP and HR during the period of stimulation were recorded, as were the maximum changes in HR and MAP from the prestimulation value (ΔHR, ΔMAP). The presence or absence of a movement response was also recorded. If the reflex movement response was vigorous, manual restraint was instituted. After 5 min to allow the HR rate and MAP to return to their prestimulation value, vecuronium bromide 1 $mg \cdot kg^{-1}$ (Organon Inc., West Orange, NJ) was administered iv in 1 ml of normal saline over 30 s. This dose is equal to the LD_{100} of vecuronium in the spontaneously breathing rat,[6] and is twice the dose necessary to produce 90% depression of twitch height.[7] The duration of action of this dose of vecuronium in the rat is between 6 and 10 min.[6,7] After a further 4 min, and following confirmation of neuromuscular blockade by the absence of an evoked twitch response, the noxious stimulus and recordings were repeated. The $F_{ET}H$ was then increased to 0.8 ± 0.05% (approximately 0.75 × MAC_H) for 30 min, and the entire sequence of stimulus-vecuronium-stimulus was repeated at the higher anesthetic concentration. The responses were assessed only at sub-MAC levels to ensure reflex movement in the absence of neuromuscular blockade and to avoid the depressor responses which occur in the rat at higher MAC levels.[8]

The maximum MAP, maximum HR, ΔMAP, and ΔHR responses to noxious stimuli in the presence of neuromuscular blockade were compared with those in the absence of neuromuscular blockade at both MAC fractions (0.6, 0.75), using one-tailed paired *t* tests. Similarly, the responses at 0.75 × MAC were compared with those at 0.6 × MAC. As multiple tests were performed on the same sample, the Bonferroni correction for multiple simultaneous comparisons was used, and only *P* values ≤ 0.01 were considered significant.[9]

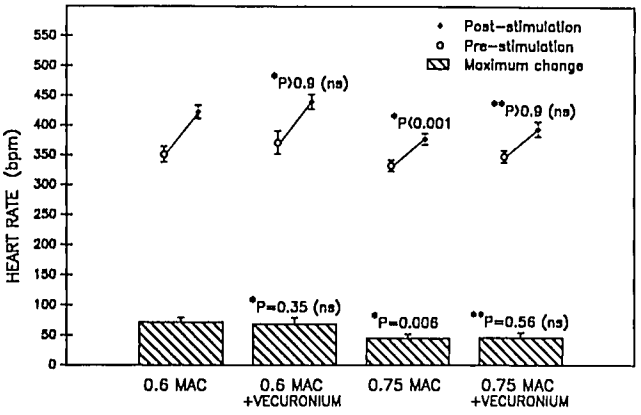

FIG. 1. Group 1 data (halothane). The effect of vecuronium on heart rate responses to noxious stimuli. *P* values obtained from one-tailed paired *t* tests comparing the variable indicated to its control (*control = 0.6 MAC, **control = 0.75 MAC, ns = not significant).

GROUP 2 (ISOFLURANE)

The experiment was repeated in additional rats (weight = 474 ± 17 g, mean ± SEM, n = 10) using the same MAC fractions (0.6 × MAC = 0.8 ± 0.05%, 0.75 × MAC = 1.05 ± 0.05%) of isoflurane (I) (MAC_I = 1.38%).[5] However, in the isoflurane group, the sequence was randomized to allow 50% of the rats to commence at 0.6 × MAC and increase to 0.75 × MAC (as in group 1), and the remainder to commence at 0.75 × MAC and reduce to 0.6 × MAC. The sequence was randomized in the isoflurane group to determine whether the reductions of the hemodynamic response caused by increasing the anesthetic concentration (which we observed in the halothane group, see Results), were independent of the order in which the two anesthetic concentrations were assessed.

Results

Prior to the administration of vecuronium, all the rats studied had a reflex movement response to tail clamp, at both MAC fractions. The administration of vecuronium prevented all movement (including respiratory efforts) and abolished the evoked twitch response for approximately 10 min in all rats.

GROUP 1 (HALOTHANE)

Figure 1 displays the effect of neuromuscular blockade with vecuronium on the prestimulation HR, the maximum HR during tail clamp, and ΔHR (maximum minus prestimulation) produced by tail clamp. The addition of neu-

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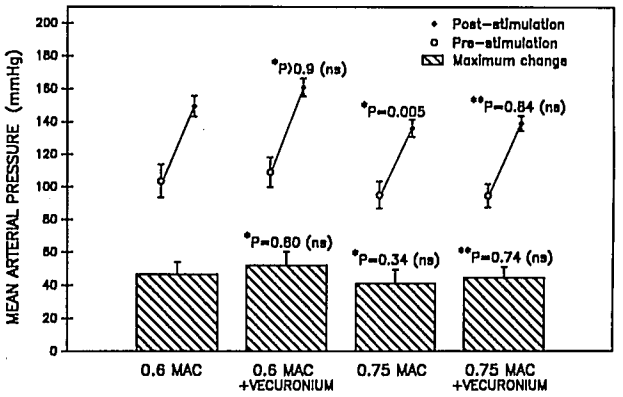

FIG. 2. Group 1 data (halothane). The effect of vecuronium on mean arterial pressure responses to noxious stimuli. *P* values obtained from one-tailed paired *t* tests comparing the variable indicated to its control (*control = 0.6 MAC, **control = 0.75 MAC, ns = not significant).

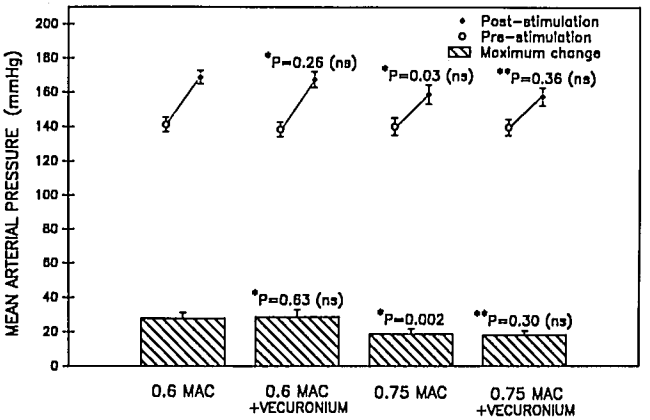

FIG. 4. Group 2 data (isoflurane). The effect of vecuronium on mean arterial pressure responses to noxious stimuli. *P* values obtained from one-tailed paired *t* tests comparing the variable indicated to its control (*control = 0.6 MAC, **control = 0.75 MAC, ns = not significant).

romuscular blockade did not reduce any of these variables, at either anesthetic concentration. However, increasing the $F_{ET}H$ from 0.6 × MAC to 0.75 × MAC did produce statistically significant reductions in both the maximum HR response ($P < 0.001$), and the ΔHR response ($P = 0.006$). Figure 2 displays similar data for MAP. The addition of neuromuscular blockade did not reduce any of the MAP responses to tail clamp. However, increasing the anesthetic concentration from 0.6 × MAC to 0.75 × MAC was associated with a statistically significant reduction in the maximum MAP response to tail clamp ($P = 0.005$).

GROUP 2 (ISOFLURANE)

Figures 3 and 4 display the data for the isoflurane group. The isoflurane group had higher values for HR and MAP than the halothane group. However, the differences were greater for the prestimulation values than for the maximum values during tail clamp. As such, the ΔHR and ΔMAP responses to tail clamp were smaller in the isoflurane group. The results were otherwise similar to the halothane group. The addition of neuromuscular blockade did not reduce any of the hemodynamic responses to tail clamp. However, increasing the $F_{ET}I$ from 0.6 × MAC to 0.75 × MAC was associated with statistically significant reductions in the maximum HR response ($P = 0.002$, fig. 3) and the ΔMAP response ($P = 0.002$, fig. 4).

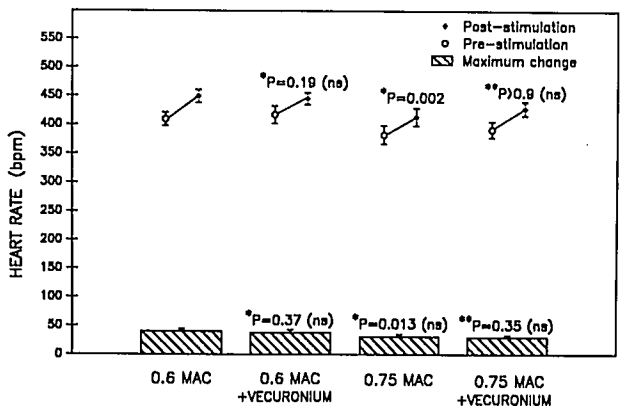

FIG. 3. Group 2 data (isoflurane). The effect of vecuronium on heart rate responses to noxious stimuli. *P* values obtained from one-tailed paired *t* tests comparing the variable indicated to its control (*control = 0.6 MAC, **control = 0.75 MAC, ns = not significant).

Discussion

Ever since the introduction of neuromuscular blocking drugs into anesthesia, there has been interest in the possibility that they possess anesthetic effects in addition to their neuromuscular blocking effects. However, it was not until 1979 that Forbes *et al.* demonstrated that pancuronium reduced the MAC of halothane by 25% in humans.[3] This study was performed by using tourniquets to isolate three limbs of each patient from the circulation. This allowed patients to move in response to skin incision. The authors postulated that the mechanism of the reduction in MAC was either a direct central effect of pancuronium, or an indirect effect dependent on the production of neuromuscular blockade. A direct central effect is unlikely, because pancuronium, like other neuromuscular blocking drugs, is a polar molecule which does not cross the blood brain barrier to any significant extent.[1,3] An indirect mechanism is more plausible, as neuromuscular blockade might reduce afferent input to the reticular activating system by abolishing peripheral muscle spindle activity.[3] This could reduce the central perception of all stimuli and would have a similar effect to increasing anesthetic depth. However, an indirect mechanism implies that the reduction of anesthetic requirement is due to the neuromuscular blockade *per se*, and should therefore be observed with all neuromuscular blocking drugs. Neither

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mechanism has been further investigated. Moreover, the Forbes *et al.* study has never been supported by subsequent studies in either humans or animals. On the contrary, a recent study has shown that neuromuscular blockade with vecuronium, a structurally similar molecule to pancuronium, does not reduce anesthetic requirement.[10]

We found that the addition of neuromuscular blockade with vecuronium did not reduce either the HR or the MAP response to noxious stimuli in rats anesthetized with either halothane or isoflurane. However, our model was sensitive enough to detect changes in hemodynamic response, as increasing the MAC fraction from 0.6 to 0.75 produced statistically significant reductions in several of the responses measured (figs. 1–4). Kissin and Green have shown that the attenuation of heart rate responses to noxious stimuli can be used as an alternate index of anesthetic depth in the rat.[11] The attenuation of hemodynamic responses to noxious stimuli is also a common method of assessing anesthetic depth clinically. As such, the inability of vecuronium to attenuate either the HR or the MAP response to noxious stimuli in our study suggests that neuromuscular blockade does not increase anesthetic depth in the rat.

Our results were similar in both of our study groups. Vecuronium did not produce statistically significant reductions in any of the HR or MAP responses to noxious stimuli, at either MAC fraction, in either the halothane or the isoflurane group. Moreover, the effect of increasing the MAC fraction was also similar in both groups, despite the different order in which MAC fractions were assessed. This indicated that the effect of changing the anesthetic concentration was independent of the order in which the two anesthetic concentrations were assessed. Although the results were qualitatively similar in both groups, there were differences in the absolute values of the variables between the halothane and the isoflurane group. The rats in the isoflurane group had higher heart rates and mean arterial pressures than the rats in the halothane group. This finding is consistent with a previous study which has shown that at an equivalent MAC, isoflurane produces less cardiovascular depression, and has a higher cardiovascular margin of safety than halothane in rats.[12]

The results of this study may have implications for laboratory investigation into the effect of anesthetic agents on hemodynamic responses to noxious stimuli in rats, and possibly other animals. Laboratory animals may require neuromuscular blockade to permit tracheal intubation or controlled ventilation. Our results suggest that neuromuscular blockade can be induced without attenuating hemodynamic responses to noxious stimuli. Our results support the findings of Kissin *et al.* who examined the effect of halothane on the cardiac accelerator response to noxious stimuli in dogs.[13] They found that pancuronium did not affect the cardiac accelerator response to noxious stimuli. However, they did not present the methods or the data on this aspect of their study.

In the interpretation of our results, it is important to differentiate between the effects of particular neuromuscular blocking drugs, and the effects of neuromuscular blockade *per se*. Our results apply to vecuronium, and to the effects of neuromuscular blockade. It is possible that other neuromuscular blocking drugs do affect hemodynamic responses to noxious stimuli through mechanisms which are independent of neuromuscular blockade. However, this is unlikely for reasons which have already been outlined. Similarly, the effects of neuromuscular blocking drugs on hemodynamic responses to noxious stimuli should not be confused with the well known effects of certain neuromuscular blocking drugs on baseline hemodynamic variables.[1]

In conclusion, our results indicate that neuromuscular blockade with vecuronium does not reduce hemodynamic responses to noxious stimuli in the rat. This suggests that neuromuscular blockade does not reduce anesthetic requirement in the rat.

References

1. Miller RD, Savarese JJ: Pharmacology of Muscle Relaxants and their Antagonists, Anesthesia, 2nd edition. Edited by Miller RD. New York, Churchill Livingstone, 1986, pp 889–943
2. Miller RD, Rupp SM, Fisher DM, Cronelly R, Fahey MR, Sohn YJ: Clinical pharmacology of vecuronium and atracurium. ANESTHESIOLOGY 61:444–453, 1984
3. Forbes AR, Cohen NH, Eger II EI: Pancuronium reduces halothane requirement in man. Anesth Analg 58:497–499, 1979
4. Larach DR, Schuler HG, Skeehan TM, Derr JA: Mass spectrometry for monitoring respiratory and anesthetic gas waveforms in rats. J Appl Physiol 65:955–963, 1988
5. Quasha AL, Eger EI II, Tinker JH: Determination and applications of MAC. ANESTHESIOLOGY 53:315–334, 1980
6. Waser PG, Wiederkehr H, Chang Sin-Ren A, Kaiser-Schonenberger E: Distribution and kinetics of ^{14}C-vecuronium in rats and mice. Br J Anaesth 59:1044–1051, 1987
7. Durant NN, Houwertjes MC, Crul JF: Comparison of the neuromuscular blocking properties of ORG NC45 and pancuronium in the rat, cat and rhesus monkey. Br J Anaesth 52:723–730, 1980
8. Gibbs NM, Larach DR, Skeehan TM, Schuler HG: Halothane induces depressor responses to noxious stimuli in the rat. ANESTHESIOLOGY 70:503–510, 1989
9. Wallenstein S, Zucker CL, Fleiss JL: Some statistical methods useful in circulation research. Circ Res 47:1–9, 1980
10. Sessler DI, Olofsson CI, Chow F: Lower esophageal contractility predicts movement during skin incision; Vecuronium does not decrease the MAC of halothane (abstract). Anesth Analg 67: S201, 1988
11. Kissin I, Morgan PL, Smith LR: Anesthetic potencies of isoflurane, halothane and diethyl ether for various end points of anesthesia. ANESTHESIOLOGY 58:88–92, 1983
12. Kissin I, Morgan PL, Smith LR: Comparison of isoflurane and halothane safety margins in rats. ANESTHESIOLOGY 58:556–561, 1983
13. Kissin I, Green D: Effect of halothane on cardiac acceleration response to somatic nerve stimulation in dogs. ANESTHESIOLOGY 61:708–711, 1984

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