Title: NEUROMUSCULAR BLOCKADE DOES NOT REDUCE ANESTHETIC REQUIREMENT IN THE RAT

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INTRODUCTION: It has been suggested that neuromuscular blockade (NMB) can reduce anesthetic requirement by abolishing muscle spindle afferent input to the reticular activating system[1]. To test this hypothesis in an animal model, we examined the effect of NMB with vecuronium on anesthetic requirement in the rat. As it is not possible to assess the attenuation of movement responses to noxious stimuli in completely paralyzed animals, we assessed the effect of NMB on hemodynamic responses to noxious stimuli[2].

METHODS: 10 male Sprague-Dawley rats weighing 405±13g (mean±sem) were anesthetized with 2% halothane (H) in O_2 in an induction chamber. After tracheostomy, mechanical ventilation was instituted, maintaining $F_{ET}CO_2$ at 5.0±0.5% (mean±range). Rectal temperature was servo controlled at 37°C. Carotid artery pressure was transduced, and the mean arterial pressure (MAP) and heart rate (HR) were continuously recorded. $F_{ET}CO_2$ and $F_{ET}H$ were monitored by mass spectrometry. Neuromuscular transmission was monitored by stimulation of the common peroneal nerve. After 30 minutes equilibration at 0.6xMAC_H (MAC_H=1.10%), a noxious stimulus (base-tail clamp) was applied for 60 s. The maximum MAP and HR during the period of stimulation was recorded, as was the maximum change in MAP and HR from the pre-stimulation value, and the presence or absence of movement. Vecuronium 1mg·kg^{-1} was then administered i.v. After a further 10 min. and following confirmation of NMB, the noxious stimulus and recordings were repeated. This protocol was repeated at 0.75xMAC_H. The maximum MAP, maximum HR, ΔMAP and ΔHR responses to noxious stimuli pre and post vecuronium were compared at both MAC levels, using one tailed paired 't' tests. Similarly, the responses at 0.6xMAC_H were compared to those at 0.75xMAC_H. As multiple tests were performed on the same sample only P values ≤0.01 were considered significant. The responses were only assessed at sub-MAC fractions to ensure movement in the absence of NMB, and to avoid the depressor responses which have been observed at higher MAC levels[3]. However, the lowest level of anesthesia used was still high enough to prevent awareness, as 0.6xMAC_H is greater than 'MAC-Awake' in humans[4].
The experiment was repeated in an additional 10 rats (wt=474±17g, mean±sem) using the same MAC fractions of isoflurane (I) (MAC_I=1.40%).

RESULTS: The figure illustrates the lack of effect of NMB on ΔMAP responses to noxious stimuli. The addition of NMB did not reduce any of the hemodynamic responses measured, at either MAC fraction, using either H or I. However, increasing the MAC fraction from 0.6 to 0.75 produced statistically significant reductions in several of the responses (Table).

DISCUSSION: To our knowledge, this study is the first direct laboratory investigation of the effect of NMB on anesthetic requirement. Our results demonstrate that, in contrast to increasing the MAC fraction, the addition of NMB is not associated with reductions in either MAP or HR responses to noxious stimuli in the rat. This indicates that, if the attenuation of hemodynamic responses to noxious stimuli is used as the end-point, NMB does not reduce anesthetic requirement in the rat. Hemodynamic responses are often used to assess anesthetic depth in the clinical setting. As such, the attenuation of hemodynamic responses to noxious stimuli provides a clinically relevant index of anesthetic requirement.

Despite the widespread use of neuromuscular blocking drugs, there have been few studies examining the effect of NMB on anesthetic requirement. Our results question the ability of NMB to reduce anesthetic requirement[1], and support the view that NMB does not contribute to the "anesthetic state"[5].

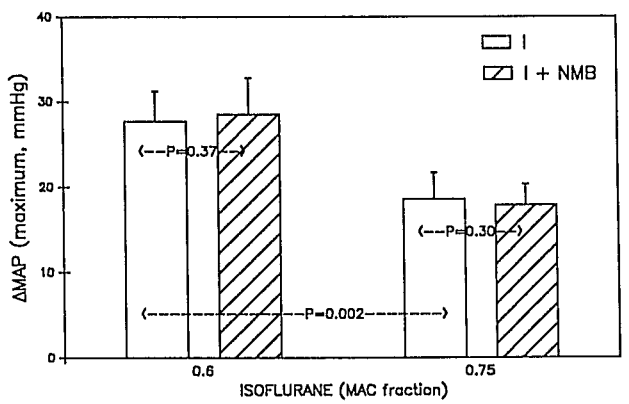

FIGURE. The effect of neuromuscular blockade (NMB) with vecuronium on ΔMAP responses to noxious stimuli in rats anesthetized with isoflurane (I). Bars indicate mean ± sem.
(P values obtained from one tailed paired 't' tests)

	HALOTHANE			ISOFLURANE		
RESPONSE	.6MAC+NMB vs. .6MAC	.75MAC+NMB vs .75MAC	.75MAC vs .6MAC	.6MAC+NMB vs .6MAC	.75MAC+NMB vs .75MAC	.75MAC vs .6MAC
ΔMAP	0.80	0.74	0.34	0.37	0.30	0.002*
ΔHR	0.35	0.56	0.006*	0.35	0.63	0.013
Max MAP	0.98	0.84	0.004*	0.26	0.36	0.03
Max HR	1.00	0.98	0.001*	0.19	0.26	0.002*

(*Indicates statistically significant reduction)

TABLE. P values obtained from one-tailed paired 't' tests comparing Hemodynamic Responses to Noxious Stimuli pre and post Neuromuscular Blockade (NMB), and pre and post increase in MAC fraction, in rats anesthetized with Halothane and Isoflurane.

REFERENCES: 1. Forbes AR, Cohen NH, Eger EI II: Pancuronium reduces H requirement in man. Anesth Analg 58:497-499, 1979
2. Kissin I, Morgan PL, Smith LR: Anesthetic potencies of isoflurane, halothane and diethyl ether for various endpoints of anesthesia. Anesthesiology 58:88-92, 1983
3. Gibbs NM, Larach DR, Skeehan TM, Schuler HG: Halothane induces depressor responses to noxious stimuli in the rat. Anesthesiology 67:A412, 1987
4. Stoelting RK, Longnecker DE, Eger EI II: Minimum alveolar concentrations in man on awakening from methoxyflurane, H, ether and fluroxene anesthesia. Anesthesiology 33:5-9, 1970
5. Cullen SC: Muscle relaxants. Anesthesiology 41:413, 1974