Laboratory Investigations

Modification by ketamine on the neuromuscular actions of magnesium, vecuronium, pancuronium and alpha-bungarotoxin in the primate

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The neuromuscular effects of ketamine, at cumulative doses of 2.5 and 10 mg · kg^{-1} iv, were studied by electromyographically quantifying the thumb response evoked by ulnar nerve stimulation in 25 monkeys anaesthetized with pentobarbital-N_2O-O_2. Ketamine alone at these doses had no neuromuscular effects. When the EMG response was maintained at 50% of control by a continuous infusion of magnesium, vecuronium, or pancuronium, ketamine depressed the responses by an additional 13 ± 3%, 34 ± 7% and 32.5 ± 3.3% (mean ± SEM), respectively, at the highest dose, $P < 0.05$. In contrast, ketamine had no effect on the neuromuscular block produced by incremental doses of alpha-bungarotoxin. These results indicate that ketamine does not act on the postjunctional acetylcholine receptor. It plays a secondary role in neuromuscular block, possibly by prejunctional or postjunctional effects independent of receptor occupation.

Les effets neuromusculaires de la kétamine, à des doses cumulatives de 2,5 à 10 mg · kg^{-1} iv, ont été étudiés en quantifiant par méthode électromyographique la réponse du pouce obtenue par la stimulation du nerf cubital chez 25 singes anesthésiés avec pentobarbital, protoxyde d'azote et oxygène. A ces doses, la kétamine seule n'avait aucun effet neuromusculaire. Lorsque la réponse électromyographique était maintenue à 50% de la valeur de base par une infusion continue de magnésium, vécuronium ou pancuronium, la kétamine diminuait les réponses d'une valeur additionnelle de 13 ± 3%, 34 ± 7% et 32,5 ± 3,3% (moyenne ± ET) respectivement, à la dose la plus élevée, $P < 0,05$. D'un autre côté, la kétamine n'avait aucun effet sur le bloc neuromusculaire produit par des doses progressives d'alpha-bungarotoxine. Ces résultats montrent que la kétamine n'agit pas sur les récepteurs postjonctionnels de l'acétylcholine. Elle joue un rôle secondaire dans le bloc neuromusculaire, possiblement par des effets préjonctionnels ou postjonctionnels indépendants de l'occupation des récepteurs.

Key words

NEUROMUSCULAR RELAXANTS: vecuronium, pancuronium;
INTERACTION: ketamine-relaxants, alpha-bungarotoxin, and magnesium sulfate.

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Ketamine is used to induce and maintain dissociative anaesthesia.[1] A number of studies have demonstrated that ketamine can potentiate the action of neuromuscular relaxants.[2–7] The main mechanism of neuromuscular action of ketamine *in vitro* has been suggested as a blockage of the acetylcholine-activated ionic channels of the motor end-plate in their open conformation.[8,9] However, the effect of ketamine on the different sites of neuromuscular junction *in vivo* has not been elucidated. We used magnesium sulfate, alpha-bungarotoxin, vecuronium and pancuronium to produce (a) inhibition of prejunctional

acetylcholine release,[10] (b) specific postjunctional acetylcholine receptor binding,[11,12] and (c) combined prejunctional[13,14] and postjunctional receptor binding, and acetylcholine-channel blockage at the end-plate, respectively. The purposes of this study were (1) to quantify the neuromuscular interaction of ketamine with these neuromuscular blockers in the primate and (2) to cast light on the mechanism of neuromuscular action of ketamine *in vivo*.

Methods

With institutional approval, 25 monkeys (Macaca cyclopis 4–5 kg) under N_2O-O_2-pentobarbital anaesthesia were studied. Induction of anaesthesia was facilitated by an intramuscular injection of pentobarbital (30 $mg \cdot kg^{-1}$). Anaesthesia was maintained with N_2O-O_2 (2:1 ratio) and a continuous intravenous infusion of pentobarbital (5 $mg \cdot kg^{-1} \cdot hr^{-1}$). Following intubation of the trachea without the use of muscle relaxant, respiration was controlled by a Harvard Apparatus® respirator for maintenance of normocarbia (PCO_2 30–40 mmHg). Oesophageal temperature was maintained at 35–37° C with a heating lamp and a thermoblanket. An anterior tibial artery was cannulated for blood pressure monitoring and blood gas determination. Arterial blood pH was 7.30–7.40. Hydration was maintained with dextrose 5% in water infused at 5 $ml \cdot kg^{-1} \cdot hr^{-1}$.

The ulnar nerve was stimulated at the wrist with supramaximal rectangular pulses of 0.2 msec duration derived from a Grass S88 stimulator. Train-of-four twitches were elicited at 2 Hz for 1.6 sec, cycled once every 12 sec. The evoked compound electromyographic (EMG) response of the first dorsal interosseous muscle of the hand was recorded using the method of Lee *et al.*[15] The two stimulating electrodes were positioned approximately 2 mm apart from each other. The two EMG electrodes were positioned sc over the muscle (the sensing) and near the tip of the thumb (the reference). The grounding electrode was placed between the stimulating and the sensing pairs of electrodes. All five electrodes were fine platinum needle electrodes made by Grass®. All study drugs were injected intravenously. Results are presented as mean ± SEM, unless otherwise stated. Wilcoxon signed rank test was used to test the differences, $P < 0.05$ being regarded as significant.

The monkeys were divided into five groups. One group ($n = 5$) received ketamine alone. Three other groups initially received magnesium sulfate ($n = 5$), vecuronium ($n = 5$) or pancuronium ($n = 5$) by a continuous infusion to maintain a constant 50% depression of the EMG for at least ten minutes. They then received 2, 3, and 5 $mg \cdot kg^{-1}$ incremental doses of ketamine added into a separate *iv* line at 5–15 min intervals, each dose injected when the effect of the preceding dose was determined. The cumulative doses of ketamine were 2, 5, and 10 $mg \cdot kg^{-1}$. The fifth group ($n = 5$) received alpha-bungarotoxin (SIGMA No. 55F-4021) prior to the injection of ketamine. The neuromuscular block produced by alpha-bungarotoxin is progressive. As a result, it is not feasible to maintain a constant steady state of neuromuscular block at precisely 50%. Therefore small doses of alpha-bungarotoxin were titrated over a period of 40–60 min to achieve a neuromuscular block which slowly proceeded from 30% to 70%. Ketamine was given at the time of 50% block. The progressive depression of the EMG by alpha-bungarotoxin during the ten minutes before and the ten minutes after the administration of each incremental dose of ketamine was compared in order to assess the neuromuscular effect of ketamine. Twenty minutes after the final dose of ketamine, 500 Tanaka units of antivenin (IVIPM FN72-05) were given *iv* over 30 min to each monkey to neutralize the excessive alpha-bungarotoxin in plasma and to avoid total paralysis. All monkeys were allowed to recover after the experiment.

Results

Ketamine alone, at the doses studied, caused no changes in the EMG response of the first dorsal interosseous muscle. However, ketamine potentiated the neuromuscular block produced by a constant infusion of magnesium sulfate, vecuronium, or pancuronium (Figure 1). The infusion rates to maintain 50% EMG depression were 1.30 ± 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$ (magnesium sulfate), 0.38 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$(vecuronium), and 0.30 ± 0.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (pancuronium), respectively. The addition of cumulative doses of ketamine up to 10 $mg \cdot kg^{-1}$ produced further depression of the EMG response in a dose-dependent manner (Figure 2). The additional depression after 10 $mg \cdot kg^{-1}$ ketamine (cumulative) was 13 ± 3% (magnesium sulfate group), 34.3 ± 7% (vecuronium group), and 32.5 ± 3.3% (pancuronium group), respectively, ($P < 0.05$ compared with the respective pre-ketamine values). In the fifth group of monkeys, incremental *iv* doses of alpha-bungarotoxin totaling 50–65 $\mu g \cdot kg^{-1}$ (57.1 ± 5.9 $\mu g \cdot kg^{-1}$) produced a 76 ± 8% final depression of the EMG response. The onset of neuromuscular block was gradual. Once the block began, a persistent slow progression followed. Progression from 25 to 50% block required 47 ± 8 min (35–65 min). The addition of ketamine had no effect on the progression (Figure 3).

Discussion

Ketamine by itself up to 10 $mg \cdot kg^{-1}$ *iv*, cumulatively, does not depress the neurally evoked compound EMG response of the first dorsal interosseous muscle of the hand in the primate. Nor does it produce train-of-four fade. Therefore, whether it occupies prejunctional or postjunctional

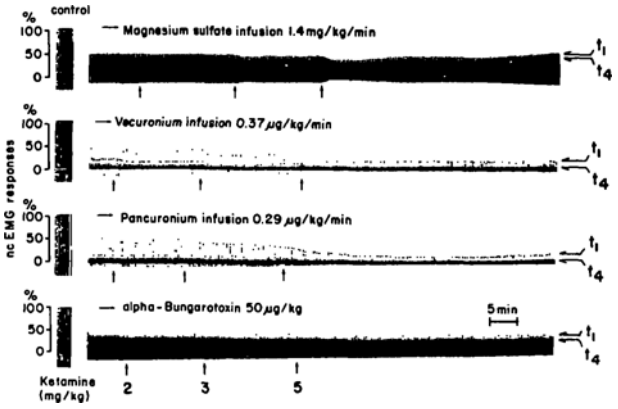

FIGURE 1 Typical ncEMG recordings to show the effect of *iv* ketamine in incremental doses of 2, 3, and 5 mg·kg^{-1} (2, 5, 10 mg·kg^{-1} cumulatively) on a constant 50% (t_1) depression produced by magnesium sulfate, vecuronium, pancuronium and alpha-bungarotoxin.

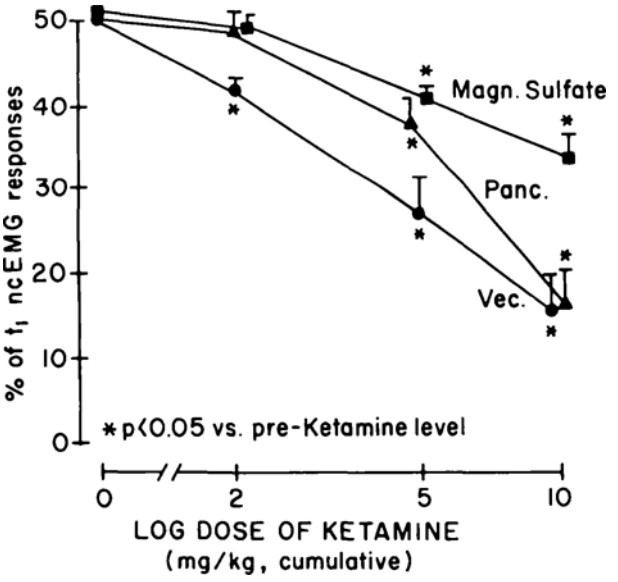

FIGURE 2 The dose-dependent effect of ketamine on a preexisting 50% neuromuscular block produced by continuous infusion of magnesium sulfate (■), vecuronium (●), and pancuronium (▲). The asterisks indicate a significant difference ($P < 0.05$) compared with pre-ketamine level. The vertical bars indicate SEM.

receptors, or occludes the acetylcholine-activated ionic channels on the end-plate, ketamine does not exhaust any physiological neuromuscular reserve. It plays only a secondary role at any of the possible action sites, and its action manifests only when primed by a preexisting similar or identical action.

Alpha-bungarotoxin produces a long-acting nondepolarizing neuromuscular block by irreversibly and specifically binding the postjunctional acetylcholine receptor.[11,12,16,17]

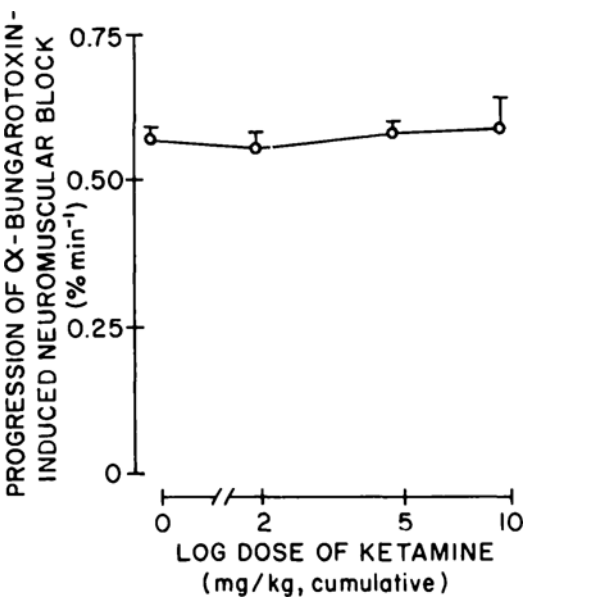

FIGURE 3 Ketamine does not affect the speed of progression of alpha-bungarotoxin-induced neuromuscular block in the private, $P < 0.05$.

During neuromuscular block produced by alpha-bungarotoxin, all postjunctional spare receptors presumably would have been occupied. Any further receptor occupation by ketamine would have enhanced the block. Our finding therefore supports the idea that ketamine does not act on the postjunctional acetylcholine receptor.

Magnesium decreases the amount of acetylcholine released by the motor impulse, reduces the sensitivity of the end-plate to externally applied acetylcholine, and depresses the direct excitability of the muscle cell membrane.[10] Its main mechanism of neuromuscular action, however, is prejunctional. The enhancement of magnesium-induced neuromuscular block by ketamine is best explained by a similar or identical prejunctional mechanism of action, according to the aforementioned argument. This prejunctional effect of ketamine agrees with Amaki,[18] who reported that ketamine at high doses decreases the presynaptic acetylcholine release in the isolated phrenic nerve-hemidiaphragm preparation of the rat. Clinically, magnesium sulfate is used to prevent seizures in the preeclamptic, to treat postoperative cardiac arrhythmia, and to prevent sickling of the red blood cells in sickle cell anaemia. Neuromuscular block may be enhanced by the concurrent administration of magnesium sulfate and ketamine to these patients.

Besides occupation of acetylcholine receptors at the end-plate, reduction of acetylcholine release, and occupation of prejunctional acetylcholine receptors, both vecuronium and pancuronium block the acetylcholine-activated

ionic channels at the end-plate, especially in high doses.[13,14] If ketamine shares any of these mechanisms of action, it will enhance the overall neuromuscular blocking effects of vecuronium and pancuronium. Our study demonstrated that ketamine did not enhance alpha-bungarotoxin-induced neuromuscular block, but caused greater potentiation of neuromuscular block produced by vecuronium and pancuronium than that produced by magnesium sulfate. The difference may be attributed to interactions with the curariform drugs at the prejunctional acetylcholine receptor sites or at the ionic channels of the end-plate where magnesium does not act. Between these two possibilities, activities of ketamine on the prejunctional acetylcholine receptors are not well defined. Activities of ketamine on the end-plate ionic channels, on the other hand, are well established. Maleque *et al.*[8] using an electrophysiological technique on the frog neuromuscular junction, concluded that ketamine blocks neuromuscular transmission mainly by interaction with acetylcholine-activated ionic channels in their open conformation. Subsequently, Wachtel[9] reported that ketamine decreased the opening time of single channel currents activated by acetylcholine. Therefore, it appears that ketamine blocks the end-plate ionic channels in the primate *in vivo*.

Recently, Lee *et al.*[19] found that ketamine prolongs the refractoriness of neuromuscular transmission. Because prejunctional depression of transmitter release by magnesium sulfate paradoxically shortens, while postjunctional depression of membrane excitability lengthens the refractory period of neuromuscular transmission, they concluded that ketamine probably depresses postjunctional membrane excitability more than it impairs acetylcholine release prejunctionally. Conceivably, the observation by Lee *et al.* may also be explained by blockage of acetylcholine-activated ionic channels in the postjunctional membrane.[8]

In summary, our study in the primate showed that ketamine potentiates the neuromuscular blocking effects of magnesium sulfate, vecuronium and pancuronium, but not alpha-bungarotoxin. These results indicate that *in vivo*, ketamine is devoid of effects on the acetylcholine receptors at the motor end-plate. The neuromuscular effect of ketamine may be attributed to a postjunctional channel-blocking action, in addition to its prejunctional effect on acetylcholine release.

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