Potentiation of Neuromuscular Blockade by Calcium Channel Blockers

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(Received October 1, 1994; Accepted October 27, 1994)

A significant reduction was noticed in the amount of vecuronium needed to maintain steady neuromuscular blockade at 20% twitch height (T1) in patients given nicardipine intraoperatively. Bolus injection of either nicardipine or diltiazem during constant infusion of vecuronium produced transient depression of T1 and the train-of-four ratio (TOFR). Reversal of neuromuscular blockade with a choline esterase inhibitor (neostigmine) was not retarded by previous administration of Ca-channel blockers but concurrent administration of anticholineesterase agent and Ca-channel blockers caused a delay in recovery from motor blockade. Monitoring of neuromuscular junction activity is strongly recommended whenever a large cumulative dose of Ca-channel blockers is used.

(Key Words: Vecuronium bromide, Ca-channel blocker, potentiation, motor blockade)

INTRODUCTION

More elderly patients, many hypertensive and under antihypertensive medication, are now being accepted for surgical treatment. Some develop bouts of dangerously high blood pressure peri-operatively and require prompt treatment. Among the maneuvers to keep blood pressure under control, the use of calcium-channel blockers in patients under anesthesia calls for special caution because these drugs may augment the effects of neuromuscular blockers which are an essential part of general anesthesia these days. We have an impression that patients managed preoperatively on calcium-channel blockers seem to require less relaxants and recover their muscular strength more slowly, suggesting that their neuromuscular junctions have been depressed by the time they come to surgery. Augmentation of muscle paralysis by calcium-channel blockers has been discussed in the literature. (1-5)

The purposes of this study were to investigate (1) whether a calcium-channel blocker, nicardipine, augments vecuronium-induced muscle relaxation, (2) whether calcium channel blockers can adversely influence the reversal of neuromuscular blockade, when given prior to or concurrently with neostigmine, and (3) whether the administration of extraneous calcium will counter-act the calcium-deprived state of the muscle and promote reversal of neuromuscular blockage.

MATERIALS AND METHODS

Study 1: Informed consent for this intraoperative study was obtained from a total of 18 female patients, over the age of 40, ASA class 1 to 2, scheduled for tympanoplasty. Seven patients developed hypertension during the operation and required nicardipine, thus automatically establishing them as the treatment group (Group 1). The remaining 11 patients did not receive a calcium-channel blocker and served as the control group (Group 2).

The effects of the calcium-channel blockers on neuromuscular blockade was documented using a Relaxograph (Datex type NMT100). To evaluate the neuromuscular blockade, the evoked action potential elicited from excited muscle fibers in response to electrical stimulation was recorded, and called "relaxograph." The stimulating electrode was placed over the ulnar nerve, and electromyogram (EMG) of the hypothenar muscles was derived using surface
electrodes. The baseline twitch height (T1) and the train-of-four ratio (TOFR, T4/T1) were obtained under light sedation with the use of intravenous thiopental and midazolam. Four submaximal peripheral nerve stimuli, at 2 Hz, were delivered and the ratio of the fourth (T4) to the first twitch amplitude (T1) was used as an index of nondepolarizing neuromuscular blockade, and is called TOFR. Anesthesia was then induced with thiopental at 2 mg/kg, followed by 0.1 mg/kg of vecuronium. Endotracheal intubation was carried out after the effect of the vecuronium had been confirmed on the Relaxograph (T1 = 0% of baseline value). After allowing T1 to recover to 15% of its initial value, the infusion of vecuronium was started. The rate of infusion was adjusted to maintain 20% of T1 throughout the surgery. Anesthesia was maintained with nitrous oxide (66%), isoflurane (0.7%), and oxygen (end-tidal). Ventilation was controlled to maintain the end-tidal CO₂ within 30-35 mmHg. (Anesthetic gas monitor Type 1304, Burel & Kjær)

If a patient developed a hypertensive episode, 0.2 to 0.4 mg of nicardipine were given intravenously.

The mean dose requirement of vecuronium for each patient was calculated when the distribution phase of the initial dose for intubation was presumed to have passed (6) and compared between the treatment and control groups. Statistical analyses were carried out by analysis of variance and Student's t-test for unpaired data, with significance set at \( p<0.05 \).

Study 2: In 8 patients (M:F = 5:3) who underwent craniotomy for clipping of an intracranial aneurysm under hypotensive anesthesia and vecuronium infusion at a constant rate, the effect of a bolus injection of either the calcium-channel blocker or calcium gluconate on muscle relaxation was observed on the Relaxograph. In cases 5 and 6, we tried to document how the calcium-channel blocker interfered with the reversal of neuromuscular blockade by neostigmine. The induction and maintenance of anesthesia were the same as in study 1, except that in all cases the calcium channel blocker was given for hypotensive anesthesia.

RESULTS

Study 1: The two groups matched well in terms of stature, body weight, body surface area, body mass index (BMI), and rectal body temperature, but there was a significant difference in the age of the two groups, being higher in the treatment group. The dose requirement of vecuronium, when normalized both for body weight and body surface area, was significantly smaller in the treatment group, \( 35\pm2 \) vs \( 43.2\pm2\) μg/kg, and \( 1.21\pm0.07 \) vs \( 1.56\pm0.11 \) mg/m² respectively. (Table 1)

No significant correlation was found between the dose requirement per unit body surface and age (\( r = 0.23 \)) in the control group.

Table 1 Demographic data and mean dose requirement (mean±SE) of vecuronium for 80% twitch suppression 1-2 hours after administration

<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BSA (m²)</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. 1</td>
<td>150.7±2.4</td>
<td>52.5±3.3</td>
<td>1.43±0.05</td>
</tr>
<tr>
<td>Gr. 2</td>
<td>150.7±1.4</td>
<td>52.4±2.5</td>
<td>1.43±0.03</td>
</tr>
</tbody>
</table>

BMI: body mass index (WT/HT²)

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Rectal temp (°C)</th>
<th>dose requirement of VB/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gr. 1</td>
<td>65±3</td>
<td>36.0±0.2</td>
</tr>
<tr>
<td>Gr. 2</td>
<td>54±1</td>
<td>36.1±0.1</td>
</tr>
<tr>
<td>p&lt;0.01</td>
<td>N.S.</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

Group 1: Treated group (\( n = 7 \)) given 1.3 mg of nicardipine intraoperatively.
Group 2: Control group (\( n = 11 \)) There were no significant differences in height, weight, body surface area (BSA), BMI, and rectal temperature, but age was significantly higher and the dose requirement of vecuronium, normalized both by body weight and BSA, was larger.
Study 2: In case 1 (male, 50 kg), 0.2 to 0.4 mg of nicardipine were given. The T1 height fell 18\%, for 30 minutes. In case 2 (female, 57 kg), 5 to 10 mg of diltiazem were given. The T1 height fell 33\% for 40 minutes. (Fig. 2) In case 3 (male, 56 kg, nicardipine) and case 4 (male, 40 kg diltiazem) bolus injections of calci-

![Graph](image-url)

**Fig. 1** No significant correlation ($r = 0.23$, $n = 13$) between age (35 to 64 yrs) and the dose of vecuronium per unit body surface area required to keep the twitch height at 20\% of control 1-2 hours after administration to untreated patients.

![Graph](image-url)

**Fig. 2** Potentiation of twitch depression by calcium channel blockers. Bolus injection of calcium channel blockers produced a slight and transient dip in T1 height during constant vecuronium infusion to maintain the steady depression of T1. Arrows indicate the injection of calcium channel blocker.

- Case 1: Ni: nicardipine
- Case 2: Di: diltiazem
- VB: vecuronium bromide
um-channel blockers suppressed both T1 (10 to 25%) and TOFR (50%). TOFR was affected to a greater degree by the blocker. (Fig. 3)

In case 5 (female, 37 kg), a total of 5 mg of nicardipine were given by continuous infusion during a 3 hour operation. When the T1 height recovered to 50% of the baseline value, 2 mg of neostigmine, in fractions, were given intravenously. Both T1 and TOFR increased and reached 100% by 17 minutes, without any delay. In case 6 (female, 54 kg), recovery of TOFR was slow following the intravenous administration of 2.5 mg of neostigmine. One mg of nicardipine was given to alleviate elevation of blood pressure upon emerging from anesthesia. (Fig. 4)

In case 7 (male, 65 kg), 2.2 mg of nicardipine and in case 8 (male, 55 kg), 25 mg of diltiazem were administered during surgery. In both cases, 425 mg of calcium gluconate was given to raise serum Ca²⁺ following massive transfusion. The extra calcium appeared to accelerate the reversal of neuromuscular blockade by counteracting the effect of the calcium-channel blockers. (Fig. 5)

**DISCUSSION**

Factors such as temperature, acid-base balance, and inhalational anesthetics, can modify the action of neuromuscular blocking agents. Calcium-channel blockers are a new addition to the list of modifiers. In study 1 (patients undergoing tympanoplasty), there was a significant difference in the doses of neuromuscular blocker needed to maintain an 80% depression of T1 in the two groups. However, because the individuals in group 1 were those who developed hypertension intraoperatively necessitating treatment, they were significantly older than the controls. It may be explained that older people require less relaxant because they clear the relaxant less efficiently. On the other hand, age alone does not adequately explain the difference between the groups. No significant correlation was found between age and dose requirement, normalized by either body weight or body surface area, in 13 patients in the control group.

The mechanism of potentiation of neuromuscular blockade is not clear. The results of
Fig. 4 The influence of calcium channel blockers on reversal of neuromuscular blockade.
Case 5: After a total of 5 mg of nicardipine was infused during a 3-hour operation, both twitch height and TOFR recovered promptly following reversal of neuromuscular blockade by neostigmine.
Case 6: During the reversal of neuromuscular blockade, nicardipine was administered intermittently to control rising blood pressure. Recovery of both twitch height and TOFR was delayed.
NSTG: neostigmine
Ni: nicardipine
VB: vecuronium bromide

This study suggests that the calcium-channel blockers act at presynaptic and postsynaptic sites because they depressed T1 and TOFR. Depression of T1 probably resulted from their action on postsynaptic nicotinic acetylcholine receptors and related ion channels (9, 10). Nicardipine and diltiazem, being L-type calcium channel blockers, are unlikely to conjugate and suppress the presynaptic nerve terminal N-type calcium channels which are related to the pulse-evoked release of acetylcholine (11). In addition, the calcium ion flux itself, through L-type calcium channels in skeletal muscle membranes, probably plays only a minor part, if at all, in producing the evoked compound action potential which we recorded with the Relaxograph. Moreover, Anderson (12) showed in feline neuromuscular preparations that the blockade was potentiated by calcium channel blockers almost to the same extent, either with 0.1 Hz electrical nerve-stimulation or with acetylcholine. This supports the assumption that the T1 depression by calcium-channel blockers is caused by their action on postsynaptic rather than presynaptic sites. Depression of TOFR is thought to reflect inhibition of regenerative release of acetylcholine from presynaptic neural endings (13). Therefore, the observed depression of TOFR was probably the result of the action of the calcium blockers on acetylcholine receptors related to the regenerative release of acetylcholine itself or to L-type calcium channels (14). The prior use of calcium channel blockers does not affect the reversal of neuromuscular blockade with neostigmine. However, if the calcium channel blocker is given concurrently with neostigmine, the reversal may take longer. Administration of the calcium gluconate restored T1 height without influencing TOFR. The Ca++ usually has no effect on neuromuscular blockade in the absence of calcium channel
Fig. 5 The influence of Ca^{++} on twitch height (T1) and TOFR shortly after the intraoperative administration of calcium channel blockers.
Case 7: Calcium gluconate (425 mg) was administered after a total dose of 2.2 mg of nicardipine.
Case 8: Calcium gluconate (425 mg) was administered after a total dose of 25 mg of diltiazem.
In both cases, twitch height increased following injection of calcium gluconate.
VB: vecuronium bromide

blockers. However, the Ca ion may potentiate the twitch response by increasing Ca^{++} influx through presynaptic calcium channels related to pulse-evoked release of acetylcholine or by acting on post-synaptic nicotinic acetylcholine-activated receptor channels. Much cannot be expected from the administration of Ca^{++} preparations to hasten reversal of the neuromuscular blockade previously potentiated by calcium channel blockers (15).

We conclude that, although calcium channel blockers administered peri-operatively do not cause serious interference with neuromuscular blockade in most cases, the use of a nerve stimulator to monitor the evoked responses is strongly recommended in cases where a fairly large amount of calcium channel blockers are administered during an operation. The time needed for restoration of muscle relaxation may be prolonged, especially when calcium channel blockers are given during the reversal of neuromuscular blockade with anticholinesterase agents.

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