Neuromuscular Blocking Drugs Do Not Alter the Pupillary Light Reflex of Anesthetized Humans

Andrew T. Gray, MD, PhD; Sharon T. Krejci; Merlin D. Larson, MD

Objective: To test the hypothesis that systemically administered neuromuscular blocking drugs acutely alter resting pupil size or the direct reflex response to light in anesthetized humans.

Design: Patients were randomized to receive an intravenous injection of saline (0.15 mL/kg), pancuronium bromide (0.1 mg/kg), or vecuronium bromide (0.15 mg/kg) after induction of general anesthesia and tracheal intubation.

Setting: The University of California, San Francisco, Moffitt-Long Hospitals.

Patients: Healthy adults (American Society of Anesthesiologists physical status I or II) of either sex scheduled for elective surgery requiring general anesthesia, tracheal intubation, and muscle relaxation of an anticipated duration of 2 or more hours.

Main Outcome Measures: Measurements of resting pupil size, direct reflex response to light, and constriction velocity were obtained in double-blinded fashion using infrared pupillometry.

Results: Pupillary size, reflex amplitude, and constriction velocity were not altered by the presence of either vecuronium or pancuronium. Tetanic stimuli and concomitant isoflurane administration respectively increased and decreased pupillary light reflex amplitude, indicating that pupillary responses were not fixed.

Conclusion: We conclude that systemically administered neuromuscular blocking drugs (vecuronium and pancuronium) do not acutely affect the pupillary light reflex in healthy, anesthetized patients.

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The pupillary light reflex is an important indicator of intact midbrain function and can help differentiate among causes of coma. However, interpretation of this reflex is often confounded by administration of drugs whose effect on the reflex is unknown. For example, neuromuscular blocking drugs are sometimes administered to critically ill patients with evolving neurologic deficits. Any effect that these paralyzing drugs might have on the light reflex would have clinical importance.

Our current knowledge of the effects of neuromuscular blocking drugs on the light reflex consists only of anecdotes and clinical impressions. Sir Benjamin Brodie, who first described the value of artificial respiration in curarized animals over 125 years ago, noted that the “pupils of the eyes were observed to contract and dilate on the increase or diminution of light.” Sir Benjamin Brodie, who first described the value of artificial respiration in curarized animals over 125 years ago, noted that the “pupils of the eyes were observed to contract and dilate on the increase or diminution of light.”

Scott Smith, a physician who allowed himself to be paralyzed to investigate possible analgesic properties of curare, was found to have “intact pupil reflexes” during complete paralysis. However, the more recent literature describes the absence or inhibition of the light reflex in response to neuromuscular blocking drugs. In addition, some neuromuscular blocking drugs have antimuscarinic properties and, therefore, the potential to alter the light reflex because it is mediated by muscarinic receptors at the pupillary sphincter.

We tested the hypothesis that systemically administered neuromuscular blocking drugs or their autonomic side effects acutely alter resting pupil size or the direct reflex response to light in anesthetized humans. Specifically, we used infrared pupillometry to quantify the effects of the neuromuscular blocking drugs pancuronium bromide and vecuronium bromide on the human pupillary light reflex.

Species differences in pupillary physiology and pharmacology are known to exist. The iris of birds and reptiles have stri-
PATIENTS AND METHODS

PATIENT SELECTION

These studies were approved by the University of California, San Francisco, Committee on Human Research. All patients gave written, informed consent. We studied 20 patients scheduled to undergo elective surgery at the Moffitt-Long Hospitals of the University of California, San Francisco. Patients were healthy (American Society of Anesthesiologists physical status I or II), of either sex, between the ages of 18 and 85 years, free of eye disease, within 30% of ideal body weight for height, and scheduled for elective surgery requiring general anesthesia, tracheal intubation, and muscle relaxation of anticipated duration of 2 or more hours. We excluded patients whose responses to any of the administered drugs might be abnormal, including patients with renal or hepatic dysfunction and those with electrolyte abnormalities. We also excluded patients with diabetes, because their light reflexes often are diminished or absent. After enrollment in the study, the patients were randomized to receive an intravenous injection of saline, vecuronium, or pancuronium.

ANESTHETIC TECHNIQUE

Patients were premedicated with fentanyl citrate (0.5-1.0 μg/kg). Anesthesia was induced by intravenous bolus injection of propofol (1-2 mg/kg) and fentanyl citrate (1.5 μg/kg) and maintained by an intravenous infusion of propofol at 100 μg·kg⁻¹·min⁻¹ and fentanyl citrate at 2 μg·kg⁻¹·h⁻¹. Succinylcholine chloride (1 mg/kg), an ultra-short-acting paralytic drug, was used to facilitate intubation of the trachea. Nitrous oxide and oxygen (7 and 3 L/min, respectively) were administered after tracheal intubation, and ventilation was controlled to maintain an end-tidal PCO₂ of approximately 32 mm Hg throughout study. If patients moved or coughed after induction of anesthesia, an additional bolus of propofol (0.5-1.0 mg/kg) was administered. Routine monitoring was used for patients undergoing general anesthesia, and the data, including blood pressure, heart rate, and end-tidal PCO₂, were recorded.

NEUROMUSCULAR BLOCKADE

At least 10 minutes after anesthetic induction, we confirmed the return of muscular function following succinylcholine paralysis for tracheal intubation with muscular twitch monitoring from surface stimulation of the ulnar nerve. We then obtained baseline measurements of the pupillary light reflex. Recording conditions were considered stable if a bolus injection of propofol had not been given for at least 10 minutes and if 3 or more scans could be taken in sequence while pupil diameter varied less than 0.2 mm. When these conditions were met, an intravenous injection of saline (0.15 mL/kg), vecuronium bromide (0.15 mg/kg), or pancuronium bromide (0.1 mg/kg) was administered. Investigators recording pupillometry data were blinded to the patient treatment group. Onset of neuromuscular blockade was verified by the absence of muscular twitch in response to ulnar nerve stimulation.

PUPILLOMETRY

Pupillary measurements were obtained using a portable infrared pupillometer (Pupilscan, Fairville Medical Optics Inc, Amersham, England) calibrated by standard means. A light stimulus of 200-millisecond duration was used for all patients, with data being collected at 20 Hz over a 2-second scan. The light stimulus was provided by 2 green light-emitting diodes having a combined light intensity of 130 candelas per square meter. All measurements were taken from the right eye, which was surrounded with a rubber cup to exclude ambient light. The left eye was taped closed with an opaque bandage.

Pupillary light reflexes were measured before induction of anesthesia and then every 15 seconds after induction until surgical skin incision (range, 10-30 minutes after administration of anesthetic agents). Preparation and draping of the patient, but no noxious stimuli, such as placement of a nasogastric tube or a Foley (urinary) catheter, were permitted during the measurement period. Scans were rejected for analysis if pupillary maximum constriction velocity exceeded 10 mm/s, indicating the presence of "noise" (10 mm/s is faster than the human pupil can constrict). To reduce noise from hand motions, 3 or more individual scans were averaged to obtain the preintervention and postintervention scans used for comparisons among the treatment groups. Specifically, data were averaged for 2 minutes before drug or saline injection and averaged within a 2-minute interval 3 minutes after drug or saline administration.

In a limited number of patients in each treatment group, after recording the preintervention and postintervention data, we added 2% isoflurane to the anesthetic regimen to determine whether the presence of an inhaled anesthetic agent might alter the light reflex response or pupillary size. Similarly, we applied a 5-second tetanic stimulus (65-70 mA) at 100 Hz to a peripheral nerve to assess the effect of a noxious stimulus on these same parameters. The study was unblinded after these measurements were completed and surgery commenced.

Treatment group demographics were compared using analysis of variance or χ² analysis of contingency tables. Differences between the effects on pupillary size, maximum constriction velocity, or light reflex amplitude of saline vs pancuronium or vecuronium before and after intervention were compared using analysis of variance. We also determined the effect size and 95% confidence intervals of differences between the pancuronium or vecuronium and saline groups. Statistical significance was inferred when the P value was less than .05.
increased the mean (± SE) heart rate and diastolic blood pressure. In addition, there was a small effect of vecuronium on diastolic blood pressure.

Figure 1 shows an example of a set of serial measurements of pupillary light reflex amplitude from one patient. Fiducial marks indicate the scale of the size of the light reflex and time during the scans. Induction of general anesthesia diminished the light reflex amplitude. Scans obtained before and after treatment were similar, indicating that vecuronium administration did not alter the light reflex amplitude. In contrast, tetanic stimulation increased the reflex amplitude, and the addition of 2% isoflurane to the anesthetic regimen induced areflexia.

Table 3 shows the average resting pupil size, light reflex amplitude, and constriction velocity before and after treatment. The effect size and 95% confidence intervals of differences from the saline group (in parentheses) are also provided. There were small (≤0.2 mm), inconsistent alterations in pupil size after all 3 treatments. The pupil dilated in 8 of the 20 patients and constricted in 12. For all patients, the mean (±SE) change in pupil size was 0.04±0.12 mm, with no individual demonstrating a change exceeding 0.25 mm. Changes in the light reflex did not differ significantly among the groups.

Figure 2 shows the average preintervention and postintervention scans for all treatment groups. The magnitude of the light reflexes was small, as expected in anesthetized patients. Similarly, changes in the light reflex after each treatment were small and inconsistent. The mean alteration of this reflex by pancuronium, vecuronium, or saline was less than 0.02 mm. The light reflex was absent, as defined by previously published criteria, in only 1 patient.

Table 4 shows the effects of postintervention tetanic stimulation and addition of isoflurane to the anesthetic regimen. These data are from 11 patients in whom there was sufficient time before skin incision to complete both tests (3, 3, and 5 patients from the vecuronium, pancuronium, and saline groups, respectively). The tetanic stimulus dilated the pupil in 10 patients, indicating that the pupils were not fixed, and the administration of isoflurane produced areflexia.

No patient sustained complications related to the study protocol. All patients of the study received neuromuscular blocking drugs as part of their anesthetic management for surgery.

Table 1. Study Demographics

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Age, y*</th>
<th>Weight, kg*</th>
<th>Height, cm*</th>
<th>Sex, M/F</th>
<th>Eye Pigment, Brown/Blue/Green</th>
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<tbody>
<tr>
<td>Pancuronium</td>
<td>48±8</td>
<td>77±7</td>
<td>166±3</td>
<td>3/3</td>
<td>4/1/1</td>
</tr>
<tr>
<td>Bromide (n=6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>45±10</td>
<td>80±11</td>
<td>167±5</td>
<td>2/5</td>
<td>5/20</td>
</tr>
<tr>
<td>Bromide (n=7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>50±6</td>
<td>68±7</td>
<td>167±3</td>
<td>2/5</td>
<td>7/30</td>
</tr>
<tr>
<td>(n=7)</td>
<td></td>
<td></td>
<td></td>
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</table>

*Data are expressed as mean (±SE).

Table 2. Monitoring Statistics*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pancuronium Bromide (n=6)</th>
<th>Vecuronium Bromide (n=7)</th>
<th>Saline (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>65±6</td>
<td>57±4</td>
<td>65±4</td>
</tr>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>72±5</td>
<td>54±4</td>
<td>62±3</td>
</tr>
<tr>
<td>Post-pre</td>
<td>7±2†</td>
<td>-3±1</td>
<td>-3±1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>103±6</td>
<td>110±15</td>
<td>105±8</td>
</tr>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>108±3</td>
<td>109±16</td>
<td>99±8</td>
</tr>
<tr>
<td>Post-pre</td>
<td>5±5</td>
<td>-1±2</td>
<td>5±3</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>60±3</td>
<td>58±6</td>
<td>64±3</td>
</tr>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>68±4</td>
<td>60±1</td>
<td>56±2</td>
</tr>
<tr>
<td>Post-pre</td>
<td>8±5†</td>
<td>2±2†</td>
<td>-8±3</td>
</tr>
<tr>
<td>End-tidal Po2, mm Hg</td>
<td>32±2</td>
<td>33±2</td>
<td>31±2</td>
</tr>
<tr>
<td>Pre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>31±2</td>
<td>33±2</td>
<td>30±2</td>
</tr>
<tr>
<td>Post-pre</td>
<td>-0.8±0.7</td>
<td>0.4±0.7</td>
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*Data are expressed as mean (±SE).

†P < 0.05.

COMMENT

We found no effect of either pancuronium or vecuronium on the pupillary light reflex at dosages producing profound neuromuscular blockade at skeletal muscle. This finding has important implications for the neurologic evaluation of paralyzed patients. Tests of midbrain function that depend on motor function, such as extraocular muscle activity, the gag reflex, or respiratory activity, are useless during complete motor blockade. The light reflex therefore represents a convenient test of midbrain function that can be detected even during the profound depression of the nervous system that accompanies general anesthesia.

Because anesthetic agents can alter the pupillary light reflex, we chose an anesthetic technique that rapidly reaches steady state. The pharmacokinetics of fentanyl, propofol, and nitrous oxide have been studied extensively. Our simulations predict that 10 minutes after bolus injections followed by intravenous infusions, plasma concentrations of propofol and fentanyl are essentially stable; ie, at 10 to 30 minutes after bolus injection, plasma propofol concentrations should vary between 1.9 and 2.0 µg/mL following a dose of 2 mg/kg and an infusion of 100 µg·kg⁻¹·min⁻¹ (STANPUMP algorithms for simulation).³,⁴ Similarly, at 10 to 30 minutes after bolus injection, plasma fentanyl citrate concentrations should vary between 1.6 and 1.7 ng/mL following a dose of 1.5 µg/kg and an infusion of 2 µg/kg·h⁻¹.¹¹ Nitrous oxide not only achieves a rapid steady state, but also has minimal effects on the light reflex response.¹² Using this anesthetic technique, we observed small variability in pupil size and light reflex amplitude in both the control and the treatment groups. We attribute these small changes to noise in the pupillomotor system, probably originating within the pupilloconstrictor nucleus.¹³
The pupillary light reflex pathway contains several synapses (ie, retina, pretectal nucleus, pupilloconstrictor nucleus, ciliary ganglion, and neuromuscular junction) that might be affected by neuromuscular blocking drugs. The first 3 synapses likely contain neuronal nicotinic acetylcholine receptors, and the pupillary sphincter contains the M3 subtype of muscarinic receptor. Pancuronium is a potent antagonist of muscarinic M3 receptors, which are expressed in cardiac tissue, and can also block other subtypes of muscarinic receptors, including the M3 receptor. Neuromuscular blocking drugs may also modulate neuronal nicotinic receptor activity.

Although the light reflex is thought to be mediated primarily through the parasympathetic pathway, some investigators have provided evidence that inhibition of the radially oriented sympathetic muscle also contributes to the light reflex. Because our study was performed in unconscious subjects, the sympathetic contribution to pupil size was either absent or negligible. It is possible that neuromuscular blocking drugs might interfere with this proposed sympathetic mechanism in awake subjects, but our study cannot address this issue. Since drug-induced muscle paralysis is not deliberately induced in awake subjects, this question is unlikely in a conventional clinical setting.

Many parameters of the human pupillary light reflex have been analyzed and are known to be affected by systemically administered drugs. Light reflex amplitude and constriction velocity are depressed by sedatives and general anesthetics. Drugs that alter sympathetic function affect redilation of the pupil after a light stimulus. Latency is thought to be altered primarily by agents that exclusively alter the parasympathetic pathway. We chose to examine pupil size and reflex amplitude because these parameters are relevant to the routine penlight examination of the pupil. We also included maximum constriction velocity because, theoretically, a light reflex having a large amplitude might not be detectable if constriction velocity is low. Other parameters, such as maximum redilation velocity, area under the curve, residual reflex after 2 seconds, and latency, were not analyzed because they are difficult or impossible to evaluate without electronic pupillometry and, therefore, are not applicable to routine clinical examination. Our averaged scans for the pancuronium, vecuronium, and saline treatment groups suggest that the effect, if any, of neuromuscular blocking drugs on the above parameters would be small (Figure 2), and significant only if large numbers of patients were studied.

Although more sensitive instruments are available, the portable infrared pupillometer is exquisitely sensi-
tive. Subtle effects on the parameters of the light reflex that we examined should be detectable with this technique, even though they might not be apparent to casual visual examination. We cannot speculate as to whether even more sensitive methods of examining the light reflex might reveal an effect of neuromuscular blocking agents on the pupil.

Certain constraints were imposed on our study by the specific drugs we chose to investigate. A study of neuromuscular blocking drugs in awake or even heavily sedated human subjects would not be ethical. The levels of neuromuscular blockade used for this study required tracheal intubation, controlled ventilation, and general anesthesia to assure the complete safety and unconsciousness of our patients. The drugs that we used to maintain anesthesia (propofol and fentanyl) are commonly used in intensive care units to provide sedation and unconsciousness. Although these drugs produce a small and poorly reactive pupil, studying the effect of neuromuscular blocking drugs under these conditions provides information that is relevant to patients both inside and outside the operating room.

Another potential limitation of this study is that we examined only healthy surgical patients. It is possible that the light reflex in patients with altered mental status or with ocular or head trauma might respond differently to neuromuscular blocking drugs; ie, conditions or events that disrupt the blood-brain barrier may increase penetration of drug into the brain. Although penetration is poor under normal conditions, the presence of sepsis or trauma may result in higher drug concentrations at central cholinergic receptors, thereby altering the light reflex. Similarly, intact blood-ocular barriers might prevent penetration of neuromuscular blocking drugs from the intravascular space to the neuromuscular junctions of the iris. However, the understanding of these barriers is poor, and the degree of exposure of the ocular muscarinic receptors to these highly ionized drugs in the systemic circulation is not known.

Neuromuscular blocking drugs are often administered to patients with neurologic deficits to facilitate diagnostic procedures such as computed tomography and magnetic resonance imaging. Our finding of no effect on pupillary parameters in healthy patients does not address the issue of safety of administration of neuromuscular blocking drugs to patients with head injury. Prophylactic neuromuscular blockade has been associated with a longer intensive care unit course and a higher incidence of pneumonia in patients with severe head injury.

We conclude that there are no acute effects of systemically administered neuromuscular blocking drugs (vecuronium and pancuronium) on the pupillary light reflex in healthy, anesthetized human subjects. We suggest that this lack of effect is attributable to their having no impact on (neither enhancing nor depressing) synaptic events in the light reflex pathway. However, our find-
ings may also be explained by the presence of competing effects at multiple sites or by the lack of delivery of neuromuscular blocking drugs to sites where these drugs might be active. To determine whether pupillary parameters are affected by the use of neuromuscular blocking drugs in patients with head trauma or sepsis or in those requiring long-term administration will require further studies.

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REFERENCES