Pancuronium Increases the Duration of Electroencephalogram Burst Suppression in Dogs Anesthetized with Isoflurane

Arthur E. Schwartz, M.D.,* Andres T. Navedo, M.D.,† Mitchell F. Berman, M.D.*

Earlier studies have demonstrated both a decrease as well as no effect on halothane MAC after administration of nondepolarizing neuromuscular relaxants. To clarify further the relationship between neuromuscular blocking agents and anesthetic potency, the authors studied the effect of pancuronium on steady-state electroencephalogram (EEG) burst suppression produced by isoflurane in dogs. Anesthesia was induced using isoflurane and oxygen via mask without the administration of other drugs. The trachea was intubated, and isoflurane was administered at a concentration sufficient to produce EEG burst suppression. Thereafter, end-tidal isoflurane concentration, temperature, and end-tidal PaO₂ were meticulously maintained at constant values. Dogs in group 1 (n = 6) received pancuronium 0.1 mg·kg⁻¹. The percent of the EEG that was isoelectric increased from 21 ± 9% (mean ± SD) to 35 ± 11% (P < 0.01). After the return of single-trace response to train-of-four stimulation, neostigmine 0.05 mg·kg⁻¹ and glycopyrrolate 0.01 mg·kg⁻¹ were administered. This resulted in a reduction in isoelectricity to 19 ± 8% (P < 0.01), similar to the value before pancuronium administration. In group 2 dogs (n = 6), the percent isoelectricity of the EEG prior to pancuronium was 25 ± 10%. After administration of pancuronium 0.02, 0.04, and 0.2 mg·kg⁻¹ sequentially, the percent isoelectricity of the EEG was 29 ± 11, 37 ± 15, and 43 ± 9%, respectively. This represents a dose-related increase in isoelectricity for the 0.04- and 0.2-mg·kg⁻¹ doses (P < 0.05). The increased duration of isoelectricity during isoflurane EEG burst suppression resulting from pancuronium administration indicates that the effect of isoflurane on the brain is enhanced by nondepolarizing neuromuscular blockade. (Key words: Anesthetics, volatile: isoflurane. Brain: electroencephalograph. Neuromuscular relaxants: pancuronium.)

There are conflicting data concerning the effects of neuromuscular blocking drugs on anesthetic requirements. Forbes and colleagues reported that administration of pancuronium reduced the minimum alveolar concentration (MAC) of halothane in surgical patients. Their study involved observation of movement after surgical incision in limbs isolated from the circulation by tourniquets. A MAC of 0.55% was measured for 17 patients who had received pancuronium (0.1 mg·kg⁻¹) compared to a MAC of 0.77% for 18 control patients. Fahey et al. repeated this study using the same tourniquet method. They failed to duplicate the results of Forbes et al. and found no difference in halothane MAC among groups that had received either no muscle relaxant, pancuronium (0.1 mg·kg⁻¹), atracurium (0.5 mg·kg⁻¹), atracurium (1.0 mg·kg⁻¹), or vecuronium (0.1 mg·kg⁻¹).

Increasing concentrations of isoflurane produce a progressive effect on the EEG from continuous EEG activity at 1 MAC to burst suppression at higher concentrations to complete electrical silence at doses greater than 2 MAC. Burst suppression is characterized by alternating periods of electrical silence disrupted by bursts of high-voltage activity. The duration of electrical silence increases with increasing anesthetic dose. The duration of EEG isoelectricity at a given anesthetic dose is a marker of anesthetic effect and is not altered by time. The current study was undertaken to determine if EEG burst suppression produced by isoflurane is modified by the administration of pancuronium.

Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee of the Health Sciences Division of Columbia University. General anesthesia was induced by inhalation of isoflurane and oxygen via mask in 12 mongrel dogs (seven male, five female) weighing 11–38 kg. Tracheal intubation was accomplished with auffed 8.0-mm endotracheal tube without the use of muscle relaxants. The dogs’ lungs were mechanically ventilated at a rate of 12 breaths/min at a tidal volume adjusted to produce an end-tidal carbon dioxide tension between 35 and 39 mmHg, as measured by infrared analysis. Venous and femoral arterial catheters were inserted, and a continuous infusion of lactated Ringer’s solution was begun (4 ml·kg⁻¹·h⁻¹). Phentylephrine was infused as needed to maintain mean arterial pressure greater than 55 mmHg. Heating pads were used to keep nasal temperature at 37.0 ± 0.5°C. Temperature, EEG, and arterial blood pressure were continuously recorded. Exhaled gas was obtained through a 16-G Teflon catheter (Angiocath®).
inserted through the endotracheal tube and positioned near the tip. Isoflurane concentration was measured by infrared analysis with a Datex CapnoMac (Helsinki, Finland). The analyzer was calibrated for each study according to the manufacturer's specifications.

The isoflurane dose was adjusted to achieve EEG burst suppression. Once a stable burst suppression pattern had been achieved, the end-tidal isoflurane concentration was held constant for each dog for the remainder of the study. The EEG signal was obtained from bifrontal platinum subdermal needle electrodes (E2; Grass, Quincy, MA). Impedances were always less than 5,000 ohms. EEG was amplified by a Neurotrac Monitor (Interspec, Clonmel, Ireland). The EEG signal was stored on analog magnetic tape with a Vetter 4 track recorder (Rebersburg, PA) and printed on a Gould recorder (model 110 2 00; Ballainvilliers, France).

After at least 90 min at a constant end-tidal concentration of isoflurane, the EEG was recorded. Dogs were assigned to one of two groups. In group 1 (n = 6), dogs received 0.1 mg·kg⁻¹ pancuronium intravenously. Then, after partial recovery from neuromuscular blockade, as documented by single-twitch response to train-of-four stimulation, neostigmine 0.05 mg·kg⁻¹ and glycopyrrolate 0.01 mg·kg⁻¹ were administered intravenously. In group 2 (n = 6), dogs received three sequential doses of pancuronium of 0.02, 0.04, and 0.2 mg·kg⁻¹ intravenously at 20-min intervals. Train-of-four stimulation preceded all EEG recordings by at least 15 min.

EEG recordings were analyzed for duration of electrical silence during a sample 5-min recording before and after administration of pancuronium or neostigmine. EEG recordings were taken from data commencing 7 min after each injection of pancuronium or neostigmine. The criteria for isoelectricity were met if there were no wave-
forms and no rhythmicity and if voltage was less than 5 μV for at least 200 ms.²,⁵

The duration of electrical silence was expressed as a percentage of the total 5-min EEG sample. Comparisons of EEG isoelectric percentage for each recording within groups was made by repeated-measures analysis of variance with Fisher’s progressive least squares differences method. Dose versus response data between groups were compared by analysis of variance. P < 0.05 was considered significant.

Results

Pancuronium 0.1 mg·kg⁻¹ abolished the twitch response to train-of-four stimulation. After administration of neostigmine, four twitches were elicited by train-of-four stimulation.

Administration of pancuronium resulted in an increased percentage of EEG burst suppression that was reversed by neostigmine. A typical EEG trace is shown in figure 1. In group 1, isoflurane was administered at an end-tidal concentration of 3.0 ± 0.4 vol% to produce EEG burst suppression. Administration of pancuronium (0.1 mg·kg⁻¹) increased the percentage of EEG that was isoelectric from 21 ± 9% to 35 ± 11% (P < 0.01). Administration of neostigmine and glycopyrrolate reversed this effect, resulting in the percentage of isoelectric EEG declining to 19 ± 8% (fig. 2) (P < 0.01 compared to the value after pancuronium administration; not significantly different from the value before pancuronium).

In group 2, isoflurane was administered at an end-tidal concentration of 2.9 ± 0.3 vol% to produce burst suppression with 25 ± 10% isoelectricity. With administration of pancuronium 0.02, 0.04, and 0.2 mg·kg⁻¹, the percentages of isoelectric EEG were 29 ± 11, 37 ± 15, and 43 ± 9.0%, respectively. All doses except the 0.02-mg·kg⁻¹ dose increased the percentage of EEG isoelectricity (P < 0.05) (fig. 3).

Comparison of the proportional changes in burst suppression between groups showed no difference in the response to the 0.1- and 0.2-mg·kg⁻¹ doses (P < 0.86). This suggests a maximum response at 0.1 mg·kg⁻¹.

Physiologic data are presented in table 1.

Discussion

Our results confirm the clinical impression that neuromuscular blockade enhances the action of general anesthetics on the central nervous system and indirectly support the original conclusions of Forbes et al.¹ that pancuronium reduces anesthetic requirement. The current results contrast with those reported by Lanier and colleagues, who administered pancuronium and neostigmine to dogs anesthetized with 0.86% end-expired halothane.⁷ They reported no changes in EEG. Furthermore, the cerebral metabolic rate for oxygen consumption, cerebral blood flow, and intracranial pressure also were unchanged. However, their analysis of the EEG was qualitative. Our study design, with the measurement of discrete isoelectric intervals, permits a quantitative analysis and therefore greater sensitivity to changes in central nervous system effect. Their use of halothane may explain the difference in results. It is also possible that in their study

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<th>TABLE 1. Physiologic Data</th>
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<td><strong>Group 1 (n = 6)</strong></td>
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<td>Control</td>
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<td>MABP (mmHg)</td>
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<td>ET_co2 (mmHg)</td>
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<td>Heart rate (beats/min)</td>
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<td><strong>Group 2 (n = 6)</strong></td>
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<td>ET_co2 (mmHg)</td>
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<td>Heart rate (beats/min)</td>
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Mean ± SD.
MABP = mean arterial pressure; ET_co2 = end-tidal CO₂ tension.
the cerebral effects of pancuronium may have been studied during a background EEG that did not permit identification of cerebral depression.

The enhancement of isoflurane EEG burst suppression by pancuronium may be mediated by neuromuscular blockade or a direct action by pancuronium on the central nervous system. The latter explanation seems highly unlikely because only trace amounts of pancuronium pass the blood-brain barrier.8 Similarly, neostigmine and glycopyrrolate do not enter the brain in appreciable quantities.9,10 Cerebrocortical activity, reflected by the EEG, more likely was modified by the alteration in proprioceptive afferent activity associated with neuromuscular blockade. This explanation is supported by reports that administration of depolarizing neuromuscular blocking drugs induces EEG arousal11,12 and is associated with increased muscle afferent activity.13 These findings suggest that nondepolarizing neuromuscular blocking drugs that reduce muscle afferent activity would have the opposite effect—reducing cerebral cortical activity. This is further supported by the antagonism of the effect of pancuronium on the EEG by neostigmine.

There is no evidence that proprioceptive activity is abolished at the level of anesthesia used in this study. Muscle afferent activity is most often measured by isolating a distal nerve branch and quantifying the positive deflections of the afferent biphasic signal above background noise. Alternatively, recordings are made from dorsal nerve rootlets of the spinal cord and validated by mechanical stretch of the associated limb.13,14 Neither of these has been shown to be abolished by administration of general anesthetics. Cortical input from motor afferent activity may be diminished by deep isoflurane anesthesia. However, even at isoflurane doses greater than 3 vol%, neuronal synaptic transmission is evident. Maclver and Roth studied in vitro dose-related effects of volatile anesthetics on synaptic responses in the rat hippocampus.15 Although depressed to 50% of control, antidromic CA1 pyramidal synaptic responses were still present during the administration of 5% isoflurane. Similarly, Miu and Puil studied inhibitory and excitatory synaptic transmission in guinea pig hippocampal neurons.16 They reported depression of the excitatory postsynaptic potential peak amplitude with the administration of 4% isoflurane but increased amplitude of the peak inhibitory postsynaptic potentials at this dose.

EEG burst suppression associated with general anesthesia is related to a reduction in the rate of cerebral metabolism. Newberg et al. demonstrated that for isoflurane there was a dose-related decrease in cerebral oxygen consumption until the onset of an isoelectric EEG.17 Thereafter, increasing concentrations of isoflurane had no further effect on cerebral oxygen consumption. In humans undergoing carotid endarterectomy treated with barbiturate to produce EEG burst suppression, cerebral lactate production was inversely related to the duration of EEG isoelectricity.18 This suggests that by enhancing isoflurane burst suppression, pancuronium may also augment the reduction in cerebral metabolic rate.

Our results cannot be explained by a time effect of isoflurane on the brain. Extensive work confirms that MAC and EEG are not altered by the duration of anesthesia. Most relevant is the work of Rampil et al., who anesthetized juvenile swine with two doses of desflurane sufficient to induce EEG burst suppression.5 The degree of burst suppression activity remained constant over time at doses of 1.5 and 1.7 MAC. Furthermore, in the current study, dogs in group 1 were administrated pancuronium 0.1 mg·kg⁻¹ at the same time that dogs in group 2 received 0.02 mg·kg⁻¹. The magnitude of the responses, however, were different. This can be accounted for only by the difference in dose and not by time. The validity of the results also do not depend on knowledge of the effect of neostigmine alone on the EEG. If neostigmine had never been administered, a dose-related effect of pancuronium on isoflurane EEG burst suppression still would have been evident. The administration of neostigmine serves only to demonstrate that the effect of pancuronium on the EEG is reversed by an antagonist of nondepolarizing neuromuscular block.

The enhancement of the electrocortical effects of isoflurane by pancuronium provides additional evidence that pancuronium may decrease anesthetic requirement. The relevance of this effect to clinical practice remains to be clarified.

References

7. Lanier WL, Milde JH, Michenfelder JD: The cerebral effects of