The Cerebral Effects of Pancuronium and Atracurium in Halothane-anesthetized Dogs

William L. Lanier, M.D.,* James H. Milde,† John D. Michenfelder, M.D.‡

Pancuronium decreases the minimal alveolar anesthetic concentration (MAC) of halothane in humans, while atracurium has a metabolite, laudanosine, which is a known cerebral stimulant. To determine if these muscle relaxants significantly alter cerebral function, their effects on cerebral metabolic rate (CMR\textsubscript{O\textsubscript{2}}), cerebral blood flow (CBF), intracranial pressure (ICP), EEG, and the cerebral energy state were studied in halothane-anesthetized dogs. Group A dogs (n = 6) were maintained at 0.86% end-expired (1.0 MAC) halothane. Thereafter, a sequence of 1) pancuronium 0.1 mg·kg\textsuperscript{-1}; 2) reversal of neuromuscular blockade with neostigmine plus glycopyrrolate; and 3) pancuronium 0.2 mg·kg\textsuperscript{-1} produced no changes in CMR\textsubscript{O\textsubscript{2}}, CBF, ICP, or EEG. Group B dogs (n = 6) also were maintained at 0.86% end-expired halothane and received the following in sequence: 1) atracurium 0.5 mg·kg\textsuperscript{-1}; 2) reversal of neuromuscular blockade with neostigmine plus glycopyrrolate; 3) atracurium 1.0 mg·kg\textsuperscript{-1}; and 4) atracurium 2.5 mg·kg\textsuperscript{-1}. There were no changes in CMR\textsubscript{O\textsubscript{2}}, CBF, or ICP; EEG evidence of cerebral arousal occurred in only one dog with the final dose of atracurium. Group C dogs (n = 6) received tetracaine spinal anesthesia and the minimal halothane concentration (mean ± SE = 0.69 ± 0.03% end-expired) that would maintain an “anesthetic” EEG pattern. Each Group C dog received the following in sequence: 1) atracurium 1.0 mg·kg\textsuperscript{-1}, and 2) atracurium 2.5 mg·kg\textsuperscript{-1}. EEG evidence of cerebral arousal occurred in all six Group C dogs. Arousal was not accompanied by significant increases in CBF, CMR\textsubscript{O\textsubscript{2}}, or ICP. In Groups B and C, neuromuscular blockade always preceded arousal. Once arousal occurred, the EEG never returned to the asleep pattern. Cerebral stimulation by atracurium in the dog is modest in magnitude, is probably independent of the neuromuscular effects of the drug, and is presumed to be secondary to the metabolite laudanosine. (Key words: Brain; blood flow; electroencephalogram; metabolism; oxygen consumption. Neuromuscular relaxants: atracurium; pancuronium.)

Although pancuronium and atracurium are large, charged molecules that should not readily cross the blood-brain barrier, these drugs may affect cerebral function. Forbes et al.\textsuperscript{3} have shown that iv pancuronium augments halothane anesthesia in humans. Atracurium, a new medium-duration relaxant, has a metabolite laudanosine\textsuperscript{2} that readily crosses the blood-brain barrier in dogs\textsuperscript{5} and produces seizures in laboratory animals.\textsuperscript{4,6} Laudanosine is rapidly produced following iv atracurium in humans;\textsuperscript{7} however, plasma elimination of laudanosine is prolonged in humans\textsuperscript{8} and dogs.\textsuperscript{9}

The following study was designed to determine if iv pancuronium and atracurium produce alterations in cerebral metabolic rates for oxygen consumption (CMR\textsubscript{O\textsubscript{2}}), cerebral blood flow (CBF), intracranial pressure (ICP), EEG, or the cerebral energy state in halothane-anesthetized dogs.

Methods

The subjects were 18 unmedicated fasting mongrel dogs weighing 12-17 kg. Anesthesia was induced with halothane in oxygen 30-40% and nitrogen and maintained with 1% end-expired halothane during surgical preparation. Succinylcholine 2 mg·kg\textsuperscript{-1} was given iv to facilitate tracheal intubation. Ventilation was controlled with a Harvard\textsuperscript{®} pump, and inspired O\textsubscript{2} was adjusted to maintain serial blood gas values (IL\textsuperscript{®} electrodes 37° C) at Pa\textsubscript{O\textsubscript{2}}, 150-200 mmHg and Pa\textsubscript{CO\textsubscript{2}}, 35 ± 0.4 mmHg (mean ± SE). Cannulae were inserted into a femoral artery for pressure measurements and into a femoral and forelimb vein for fluid and drug administration. During the preoperative period, dogs were given dextrose 5% in lactated Ringer’s solution 5 ml·kg\textsuperscript{-1}, and a continuous infusion of lactated Ringer’s solution 2 ml·kg\textsuperscript{-1}·h\textsuperscript{-1} was begun. Individual dogs were given additional infusions of dextran 5-10 ml·kg\textsuperscript{-1} during the preoperative period or phenylephrine as needed (0.04 mg·ml\textsuperscript{-1} in 0.9% saline solution) during the study period to maintain mean arterial pressure (MAP) ≥ 60 mmHg. Bicarbonate was given as needed to maintain a buffer base near 40 mEq/l.

After heparinization (with 300-400 units·kg\textsuperscript{-1} iv), the sagittal sinus was exposed, isolated, and cannulated as previously described.\textsuperscript{8} This allowed blood sampling and provided direct measurement of CBF from the anterior, superior, and lateral portions of both cerebral hemispheres, representing approximately 54% of the total brain weight.\textsuperscript{9} Blood flow was continuously recorded with the use of a square wave electromagnetic flow meter (EP 300 APP, Carolina Medical Electronics).\textsuperscript{10} Blood oxygen contents were calculated from measurement of oxyhemoglobin concentrations (CO-oximeter\textsuperscript{®}, IL 282) and...
oxygen tension (IL electrodes).\textsuperscript{11} CMRO\textsubscript{2} was calculated as the product of CBF and the arterial–sagittal sinus blood O\textsubscript{2} content difference. A six-lead, three-channel bipolar EEG was recorded from frontal, parietal, and occipital electrodes glued to the calvarium. ICP was monitored by an epidural fiberoptic device (LADD Research Industries Inc.). Brain temperature was monitored by a parietal epidural thermistor and maintained at 37.1 ± 0.0\textdegree C with heat lamps. Neuromuscular blockade was evaluated by train-of-four with the use of a MiniStim\textsuperscript{R} (Professional Instruments Co.). Needle electrodes were used to stimulate the tibial nerve, and plantar flexion of the foot was quantitated by visual inspection. Inspired and end-expired halothane concentrations were measured with an infrared analyzer (Beckman Medical Gas Analyzer LB-2\textsuperscript{R}) calibrated for halothane. The ears of all dogs were plugged with cotton, and the eyes were taped shut.

The group of dogs then was divided into three groups. Dogs from Groups A and B were maintained at 0.86\% end-expiratory halothane (1.0 MAC) during the study period. After a control period, each Group A dog (n = 6) received the following in sequence at 30-min intervals: 1) pancuronium 0.1 mg·kg\textsuperscript{-1}; 2) neostigmine 0.05 mg·kg\textsuperscript{-1} plus glycopyrrolate 0.009 mg·kg\textsuperscript{-1}; 3) neostigmine 0.02 mg·kg\textsuperscript{-1} plus glycopyrrolate 0.003 mg·kg\textsuperscript{-1}; and 4) pancuronium 0.2 mg·kg\textsuperscript{-1} plus glycopyrrolate 0.012 mg·kg\textsuperscript{-1}. Each Group B dog (n = 6) received the following in sequence at 30-min intervals: 1) atracurium 0.5 mg·kg\textsuperscript{-1}; 2) neostigmine 0.07 mg·kg\textsuperscript{-1} plus glycopyrrolate 0.012 mg·kg\textsuperscript{-1}; 3) atracurium 1.0 mg·kg\textsuperscript{-1}; and 4) atracurium 2.5 mg·kg\textsuperscript{-1} iv. In Group C dogs (n = 6), spinal anesthesia was produced with the use of an indwelling percutaneous lumbar subarachnoid catheter to immobilize the dogs and provide analgesia during periods in which they received sub-MAC halothane concentrations. Preservative-free tetracaine 0.5 mg·kg\textsuperscript{-1} in 4-ml sterile H\textsubscript{2}O was injected at 30-min intervals with the dog in the prone position until complete sensory and partial motor blockade to the level of the forelimbs was demonstrated. Spinal anesthesia level was evaluated by temporarily decreasing halothane concentrations to sub-MAC levels (0.4–0.7\% expired) and observing the withdrawal response to electric stimulation of the skin over the neck and forelimbs. Individual dogs received a total of 1.0 or 1.5 mg·kg\textsuperscript{-1} tetracaine. ICP was monitored during tetracaine injection, and injection rates were adjusted to maintain ICP < 15 mmHg and cerebral perfusion pressure ≥ 60 mmHg. Scalp incisions were infiltrated with 0.5\% lidocaine before study. The vagus nerves were sectioned in the neck to eliminate the vagal effects on the heart during light anesthesia. After recording an “anesthetic” EEG pattern at approximately 0.9\% end-expired halothane, the concentration was rapidly decreased until an “awake” EEG pattern was recorded at approximately 0.45\% end-expired.\textsuperscript{12} The “awake” pattern was identified by a stable reduction in amplitude and increase in frequency of the EEG.\textsuperscript{12,13} Next, halothane concentrations were increased by 0.01\% end-expired increments every 2–3 min until a transitional or “shifting” EEG pattern was recorded. The “shifting” EEG was identified by the appearance of high-amplitude slow waves or an equal distribution of alternating “anesthetic” and “awake” EEG patterns.\textsuperscript{12,13} Examples of the various patterns are shown in figure 1. Halothane was next increased by 0.01\% end-expired every 5 min until a stable “anesthetic” EEG pattern was recorded. This occurred at 0.55–0.75\% end-expired halothane (mean, 0.69 ± 0.03\%). Halothane concentrations then were decreased by 0.01\% end-expired every 5 min until the “shifting” EEG pattern was reidentified. Finally, halothane concentrations were increased 0.01\% end-expired every 5 min until the “anesthetic” EEG was again seen. Halothane concentrations remained at this level for 30 min before control measurements were taken. After the control period, each Group C dog received the following in sequence at 30-min intervals: 1) atracurium 1.0 mg·kg\textsuperscript{-1}; and 2) atracurium 2.5 mg·kg\textsuperscript{-1} iv.

Drug infusion rates were standardized for all groups. Pancuronium was infused at a rate of 0.1 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}, and atracurium was infused at 1.0 mg·kg\textsuperscript{-1}·min\textsuperscript{-1}. Neostigmine plus glycopyrrolate mixtures were administered as a bolus.

At the conclusion of the studies in dogs from Groups A and B, the dogs’ ears were unplugged, and the dogs
were hyperventilated to a $P_{aCO_2}$ of 22 ± 0.4 mmHg. Auditory stimulation was provided by crashing a cymbal in the dogs' ears in an attempt to elicit EEG evidence of seizure activity. Finally, normocarbia was achieved, and the dura overlying the cerebral hemispheres was excised. Cerebral biopsies from the frontal lobes were taken with the use of a punch biopsy system that deposits brain tissue into liquid nitrogen within 1 s. Each sample was analyzed using the enzymatic fluorometric techniques described by Lowry et al.15 for adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), phosphocreatine (PCr), glucose, lactate, and pyruvate. The energy charge (EC) was calculated with the use of the values for ATP, ADP, and AMP.16 Finally, dogs' brains were removed and weighed to allow expression of $CMRO_2$ and CBF as a function of brain weight.

At each measurement interval after drug interventions, physiologic responses were measured in triplicate and averaged; however, individual measurements were used to compare cerebral variables that occurred concomitant with EEG changes. The responses at each measurement period for $CMRO_2$, CBF, and ICP were later expressed as a percentage of control, and the average response was calculated for each drug intervention. Values within each group were compared with the use of paired $t$ tests. Unpaired $t$ tests were used to compare values between groups and to compare cerebral metabolic values between Group A, Group B, and our laboratory's normal values for dogs. Bonferroni's correction for $t$ tests was used when comparing more than two groups.

### Results

Control values for cerebral and systemic variables are listed in Table 1. Control $P_{aO_2}$ values were significantly, but not meaningfully, different in Group B. Control CBF values in Group C were significantly lower than in Groups A and B, as expected, because of differences in anesthetic management.

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
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<tbody>
<tr>
<td>$MAP$ (mmHg)</td>
<td>87 ± 4</td>
<td>89 ± 5</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>$P_{aO_2}$ (mmHg)</td>
<td>182 ± 2</td>
<td>158 ± 5</td>
<td>176 ± 4*†</td>
</tr>
<tr>
<td>$P_{aCO_2}$ (mmHg)</td>
<td>36 ± 1</td>
<td>35 ± 1</td>
<td>35 ± 1‡</td>
</tr>
<tr>
<td>pH</td>
<td>7.35 ± 0.01</td>
<td>7.36 ± 0.01</td>
<td>7.38 ± 0.01‡</td>
</tr>
<tr>
<td>$BB^*$ (mEq·1⁻¹)</td>
<td>41 ± 1</td>
<td>41 ± 0</td>
<td>42 ± 1‡</td>
</tr>
<tr>
<td>$CMRO_2$ (ml·min⁻¹, 100 g⁻¹)</td>
<td>4.12 ± 0.15</td>
<td>4.44 ± 0.18</td>
<td>4.53 ± 0.21‡</td>
</tr>
<tr>
<td>CBF (ml·min⁻¹, 100 g⁻¹)</td>
<td>62.8 ± 4.6</td>
<td>62.4 ± 3.9</td>
<td>2.3±§</td>
</tr>
<tr>
<td>ICP (mmHg)</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>2 ± 1‡</td>
</tr>
</tbody>
</table>

Mean ± SEM (six dogs in each group). A Bonferroni correction of $P < 0.05/3 = P < 0.016$ was considered significant.

* Group A significantly different from Group B.
† Group B significantly different from Group C.
‡ NS = no significant differences between groups.
§ Group A significantly different from Group C.

In Group B dogs, at 0.86% end-expired halothane, significant variations from the control values of $CMRO_2$, CBF, ICP were not seen after atracurium 0.5 mg·kg⁻¹.

**Fig. 2. Effects of CBF and $CMRO_2$ in Group A dogs at 1.0 MAC halothane after iv administration of 1) pancuronium 0.1 mg·kg⁻¹; 2) neostigmine 0.05 mg·kg⁻¹ plus glycopyrrolate 0.009 mg·kg⁻¹; 3) neostigmine 0.02 mg·kg⁻¹ plus glycopyrrolate 0.003 mg·kg⁻¹; or subsequent pancuronium 0.2 mg·kg⁻¹ (fig. 2). All dogs had a normal train-of-four during the control period and after the second dose of neostigmine and glycopyrrolate. Paralysis was complete after each dose of pancuronium. Variable return of the train-of-four was noted after the initial neostigmine 0.05 mg·kg⁻¹, and results were as follows: one twitch (two dogs), two twitches (two dogs), and four twitches (two dogs). EEG evidence of alterations in anesthetic depth was not seen following the various drug interventions.**
neostigmine 0.07 mg·kg⁻¹ plus glycopyrrolate 0.012 mg·kg⁻¹, atracurium 1.0 mg·kg⁻¹, and atracurium 2.5 mg·kg⁻¹ (fig. 3). Train-of-four was normal during the control period and after neostigmine plus glycopyrrolate. No twitches were observed after each dose of atracurium. In one Group B dog, the EEG changed from an “anesthetic” to an “awake” pattern during the period in which the 2.5 mg·kg⁻¹ was being infused. This was accompanied

by a mere 2% increase in CMRO₂ and a 3% increase in CBF.

Values of canine cerebral metabolites for our laboratory normals, Groups A and B, are listed in table 2. Although small but statistically significant differences were noted in ADP, glucose, lactate, and pyruvate values between various groups, there were no significant differences in ATP, AMP, EC, PCR, or L/P values.

In Group C dogs with spinal anesthesia and sub-MAC concentrations of end-expired halothane, there were no significant changes in CBF, CMRO₂, or ICP from the control period to after atracurium 1.0 mg·kg⁻¹ and 2.5 mg·kg⁻¹ (fig. 4). Atracurium produced evidence of EEG arousal in all six dogs. In one dog, this was manifested as a “shifting” EEG pattern at 9 min after the 2.5 mg·kg⁻¹ dose. In the other five dogs, an “awake” EEG pattern began 5–25 min after the 1.0 mg·kg⁻¹ dose. Progression from the “anesthetic” EEG pattern to the onset of maximum EEG arousal took from 3 to 19 min, with an average of 11 ± 3 min to evolve in the five dogs who achieved an “awake” EEG pattern. The change was instantaneous in the sixth dog, who achieved the “shifting” pattern only.

In all Group C dogs and the one Group B dog in which EEG arousal was noted, the EEG never returned to the “anesthetic” pattern once arousal began. EEG evidence of seizure activity was not seen in Groups A, B, or C in response to drug intervention, nor was seizure activity observed in Groups A and B after hyperventilation and auditory stimulation.

In Group C dogs, when the period of onset of maximal EEG arousal was compared with the preceding measurement period, CMRO₂ and CBF increased in five dogs (ranges: 1–17% and 7–24%, respectively) and decreased in the sixth dog (8 and 11%, respectively). The mean changes in CMRO₂ and CBF during arousal did not achieve significance by paired t test (fig. 5). When the period of maximum EEG arousal was compared with the measurement period in which the EEG last resembled the control, “anesthetic” EEG, CMRO₂ during arousal in-

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**TABLE 2. Biopsy Results for Cerebral Metabolites—Groups A, B and Previously Determined Laboratory Normal Values Are Compared**

<table>
<thead>
<tr>
<th></th>
<th>Laboratory Normals</th>
<th>Group A (Pancuronium)</th>
<th>Group B (Atracurium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP (µmol·g⁻¹)</td>
<td>2.01 ± 0.01</td>
<td>2.08 ± 0.07</td>
<td>1.91 ± 0.12*</td>
</tr>
<tr>
<td>ADP (µmol·g⁻¹)</td>
<td>0.375 ± 0.009</td>
<td>0.476 ± 0.032</td>
<td>0.418 ± 0.025†</td>
</tr>
<tr>
<td>AMP (µmol·g⁻¹)</td>
<td>0.138 ± 0.004</td>
<td>0.127 ± 0.005</td>
<td>0.132 ± 0.010*</td>
</tr>
<tr>
<td>EC</td>
<td>0.87 ± 0.00</td>
<td>0.86 ± 0.01</td>
<td>0.86 ± 0.01*</td>
</tr>
<tr>
<td>Glucose (µmol·g⁻¹)</td>
<td>2.46 ± 0.18</td>
<td>1.95 ± 0.21</td>
<td>1.85 ± 0.12‡</td>
</tr>
<tr>
<td>PCR (µmol·g⁻¹)</td>
<td>2.99 ± 0.12</td>
<td>3.64 ± 0.20</td>
<td>3.34 ± 0.31*</td>
</tr>
<tr>
<td>Lactate (µmol·g⁻¹)</td>
<td>1.28 ± 0.04</td>
<td>1.90 ± 0.26</td>
<td>1.85 ± 0.15‡†</td>
</tr>
<tr>
<td>Pyruvate (µmol·g⁻¹)</td>
<td>0.117 ± 0.004</td>
<td>0.132 ± 0.006</td>
<td>0.136 ± 0.005‡</td>
</tr>
<tr>
<td>L/P</td>
<td>11 ± 0</td>
<td>15 ± 1</td>
<td>14 ± 1*</td>
</tr>
</tbody>
</table>

Mean ± SEM (six dogs in each group). A Bonferroni correction of P < 0.05/3 = P < 0.016 was considered significant.

* t:S = No significant differences between groups.

† Group A significantly different from normals.
‡ Group B significantly different from normals.
creased in five dogs (range 1–17%) and decreased in one dog (5%). Cerebral blood flow increased in three dogs (range 17–57%) and decreased in three dogs (range 8–11%). Again, the mean changes in CMRO₂ and CBF failed to achieve significance by paired t test (fig. 5).

Discussion

Neuromuscular blocking drugs are large charged molecules that do not readily cross the blood–brain barrier, however, cerebral effects of intravenously administered depolarizing and nondepolarizing drugs have been reported. In general, depolarizing relaxants tend to stimulate the brain, while nondepolarizing relaxants tend to augment anesthetic depth. These findings are best explained by the afferent muscle spindle theory, which predicts that agents or maneuvers that actively or passively cause muscle stretch or contraction will stimulate the brain. Agents that inhibit muscle stretch or contraction may decrease cerebral activity. Induction of depolarizing neuromuscular blockade by succinylcholine, decamethonium, and carbolonium have been shown to induce

Fig. 5. CMRO₂ and CBF values concomitant with EEG changes in Group C dogs (sub-MAC halothane concentrations). The period of "arousal" was not significantly different from the three earlier measurement periods at the Bonferroni corrected value of $P < 0.05 / 3 = P < 0.016$. Vertical bars represent the standard error of the mean.

■ = control; □ = last "anesthetic" EEG; □ = before arousal; □ = arousal.

EEG arousal; however, arousal is prevented by prior administration of the nondepolarizing relaxants gallamine and alcuronium. The anesthesia-augmenting effects of pancuronium were demonstrated by Forbes et al., who showed a reduction in halothane MAC in humans from 0.73 to 0.55% end-expired. Hodes also has shown that gallamine produced electrocortical synchronization in anesthetized cats when administered iv but not when injected into the carotid arteries. After the effects of iv gallamine had dissipated, electrocortical synchronization readily was reinitiated by small doses of barbiturate.

Pancuronium did not affect the cerebral variables measured in this study in dogs at one MAC halothane anesthesia. This negative finding, however, does not disagree with the findings of Forbes et al. If we assume that the anesthetic-augmenting effect of pancuronium is equivalent to an additional 0.18% end-expired halothane,
Group A dogs should exhibit the cerebral effects of 1.04% end-expired halothane. Stullken et al. (unpublished data) have shown that increasing halothane concentrations from 0.85 to 1.05% end-expired should decrease CMRO₂ and CBF by less than 1%. Thus, any cerebral effect of pancuronium at 0.86% end-expired halothane, if present, was of insufficient magnitude to be detected by our protocol.

Electroencephalogram evidence of cerebral arousal following atracurium represents an unusual response for a nondepolarizing relaxant and cannot be explained by the afferentation theory. Therefore, we must assume this effect was due to factors other than neuromuscular blockade. One must consider the possibility of EEG “drift” during the study secondary to changes in anesthetic depth. “Drifts” in anesthetic depth should have been more important in Group C animals at 0.69% halothane than in Groups A and B at 0.86% halothane because the level of anesthesia in Group C more closely approached the level required to produce a shifting EEG pattern. The “drift” theory does not explain arousal in one Group B dog. Also, it does not explain the observation that in the one Group B dog exhibiting arousal and in all six Group C dogs sustained EEG arousal never was seen during the control period or immediately after administration of the initial dose of atracurium. However, once arousal began, all seven animals who manifested arousal patterns never returned to an “anesthetic” EEG pattern. This is unusual, considering the fact that the one Group B dog had maintained an anesthetic pattern for more than 100 min before arousal and the six Group C dogs had individually maintained an “anesthetic” EEG pattern for periods in excess of 35–69 min before arousal. Furthermore, in Group C animals, halothane concentrations were increased before the control period so that if any anesthetic “drift” occurred secondary to equilibration between the alveoli and brain, anesthesia would proceed to a deeper plane of anesthesia and away from the “shifting” EEG. We conclude that anesthetic “drift” was unlikely in any of the three groups, particularly as the halothane levels remained stable for prolonged periods before control measurements and did not measurably change thereafter.

The cerebral effects of atracurium-induced histamine release also must be considered. Histamine release after iv atracurium is approximately one-third the amount seen after iv d-tubocurarine. Electroencephalogram arousal in laboratory animals has been reported by Monnier et al. after histamine infusions into the jugular vein and into the third ventricle. Crossland and Mitchell noted cerebellar electrical stimulation after intracarotid histamine injections. These studies concluded that histamine possesses a direct stimulating effect on the brain; however, this interpretation must be questioned. Histamine does not cross the blood–brain barrier, and cortically applied histamine has no effect on the EEG. It is unlikely the cerebellar stimulation noted by Crossland and Mitchell was directly due to histamine because the electrical effects were delayed, and the cerebellum probably lacks histamine receptors. Histamine iv is known to alter cardiopulmonary dynamics resulting in hypercarbia. The magnitude of hypercarbia reported after iv administration of d-tubocurarine has been shown to produce EEG amplitude decreases and frequency increases consistent with arousal. Hypercarbia after iv d-tubocurarine is presumably secondary to histamine, since diphenhydramine pretreatment blocks the PₐCO₂ response. As the methods of Monnier et al. and Crossland and Mitchell used histamine doses greatly in excess of those shown to produce immediate cerebrovascular alterations, and their methods allowed histamine to eventually enter the pulmonary circulation, we conclude that the delayed EEG effects they observed were secondary to hypercarbia. Unfortunately, none of the studies used blood gas analysis. Intracranial pressure increases after administration of d-tubocurarine or histamine probably result from both histamine-induced increases in PₐCO₂ and a potent direct vasodilating effect of histamine. Because blood gases frequently were measured and rigorously controlled during our study, and ICP and CBF did not significantly increase during any measurement period, we conclude that EEG changes in dogs from Groups B and C were not secondary to histamine release.

Arousal is best understood when one examines the metabolism of atracurium. Atracurium is metabolized by two processes, ester hydrolysis and Hofmann elimination, a temperature and pH-dependent enzymatic process. Laudanosine, a Hofmann elimination metabolite of atracurium, is a benzylisoquinoline alkaloid found in opium. Laudanosine previously has been reported to cause seizures in frogs, rabbits, and dogs. In 1955, Mercier and Mercier reported mild EEG arousal in ether-anesthetized dogs after administration of laudanosine 2–5 mg·kg⁻¹ iv, while doses of 9–10 mg·kg⁻¹ produced seizures. That atracurium produced arousal but not seizures in some, but not all, of our dogs can be explained by the following. First, Prince and Shazer showed that the cerebral response to stimulation is affected by anesthetic depth. This was confirmed in our study in which all six Group C dogs at sub-MAC halothane levels showed EEG evidence of arousal after atracurium, while this effect was seen in only one of six Group B dogs at 1.0 MAC halothane, and then only at cumulative atracurium doses greater than that given any Group C dog. Secondly, laudanosine production by clinical doses of atracurium was probably insufficient to produce seizure activity in healthy dogs. The molecular weight of atracurium is 1243.49, and the molecular weight...
of laudanosine is 357.43. Therefore, if metabolism occurred only by the Hofmann elimination route, and a maximum of two molecules of laudanosine were produced from the breakdown of each atracurium molecule, a maximum of 0.57 mg laudanosine could be produced from each milligram of atracurium. Although the anesthetic depth was not discussed in the Mercier and Mercier article, we assume that doses of atracurium in excess of 15 mg·kg⁻¹ would be required to produce the quantity of laudanosine required for seizure production in their study.

Fahey et al. have shown that peak plasma laudanosine levels in humans occur 2 min after an iv bolus of atracurium and remain at approximately 75% of peak levels or greater for 15 min after the atracurium bolus. Therefore, laudanosine levels begin to slowly decline. Because laudanosine production from atracurium is entirely dependent on Hofmann elimination, a nonenzymatic process, laudanosine production in dogs should not significantly differ from that in humans. Hennis et al. have shown that cerebrospinal fluid concentrations of laudanosine in dogs were maximal 3–10 min after an iv bolus of laudanosine. Extrapolations from these data lead us to assume that EEG arousal would most likely occur 5–25 min after an initial dose of atracurium, provided laudanosine production was adequate to produce arousal. Arousal by subsequent doses of atracurium would not be expected to follow this time frame because cerebral accumulation of laudanosine from previous atracurium administration might shorten the time to arousal onset. Our results support the above assumptions. Five of six Group C dogs exhibited EEG arousal after an initial atracurium dose, and arousal began 5–25 min after completion of atracurium in all five. In the single dogs in Groups B and C who exhibited arousal with subsequent doses of atracurium, the Group B dog exhibited EEG arousal during the 2.5-min period in which atracurium was being infused, and the Group C dog exhibited arousal 9 min after completion of atracurium infusion.

Neuromuscular blockade by atracurium always preceded arousal in our dogs. By the afferentation theory, nondepolarizing neuromuscular blockade would be expected to partially offset the cerebral-stimulating effects of laudanosine. After an initial dose of relaxant in dogs from Groups A and B, reversal of neuromuscular blockade with neostigmine and glycopyrrolate was initiated in an attempt to "unmask" the cerebral effects of any active relaxant metabolites. Neostigmine was chosen since it is a quaternary amine compound that does not enter the brain in appreciable quantities. Horrigan has shown that large doses of iv neostigmine caused a decrease in halothane MAC in dogs; however, neostigmine doses comparable to those used in our study (0.04 mg·kg⁻¹ in their study vs. 0.07 mg·kg⁻¹ in our study) produced no significant changes in MAC. Furthermore, neostigmine was given to unparalyzed dogs in the Horrigan study, while our dogs received neostigmine during periods of nondepolarizing neuromuscular blockade. By the afferentation theory, reversal of neuromuscular blockade should result in relatively increased cerebral stimulation. Glycopyrrolate, a quaternary ammonium anticholinergic agent, was chosen because it does not readily cross the blood-brain barrier and it apparently does not produce the sedative effects noted with atropine.

In our study, the combination of neostigmine and glycopyrrolate produced no changes in EEG, CBF, CMRO₂, or ICP in dogs from Groups A and B, whether the combination was given in a fashion in which train-of-four return was incomplete (Group A) or complete (Groups A and B). Therefore, we conclude that the neostigmine–glycopyrrolate combination had no cerebral effects of its own in paralyzed dogs, nor was reversal of neuromuscular blockade capable of "unmasking" the arousal effects of laudanosine. It is possible that laudanosine production by atracurium 0.5 mg·kg⁻¹ was insufficient to produce cerebral stimulation. Attempts to reverse the blockade produced by larger doses of atracurium in pilot dogs proved unsuccessful within the time limits of the study.

Electroencephalogram arousal by atracurium was accompanied by a tendency toward increasing CMRO₂ and CBF, however, neither change was statistically significant. The trend toward increased CMRO₂ agrees with the study of Stulken et al., who showed that CMRO₂ decreased from 4.45 to 3.96 ml·min⁻¹·100 g⁻¹ (11%, P < 0.01) when proceeding from an "awake" to an "anesthetic" EEG pattern, however, CBF did not change. In that study, EEG shifts were accomplished by changing halothane concentrations and not by adding an arousal agent to a constant level of halothane anesthesia. It is uncertain whether this would affect the magnitude of changes in our study or not. There are other differences between the Stulken et al. study and ours that may have affected the findings. Their measurements were performed as anesthesia changed from a level of lesser to greater depth, and the opposite was true in our study. Thus, there is a possibility of hysteresis between EEG, halothane concentrations, CMRO₂, and CBF. We examined for the possibility of hysteresis between expired halothane and EEG patterns. The interface between the "shifting" and "anesthetic" EEG patterns occurred at the same halothane

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§ Hill PK: Personal communication, Burroughs Wellcome Co.

1 Stulken EH, Michenfelder JD: Unpublished data.
concentrations whether halothane concentrations were increasing or decreasing, provided 10–15 min were allowed for equilibration between the alveoli and the brain. This observation confirms the calculations of Eger et al., that, based on solubility coefficients, a 15-min interval is required for 95% equilibration of arterial and brain tensions for halothane. In pilot dogs, hysteresis was observed with more rapid changes in exhaled halothane with greater hysteresis occurring with more rapid changes in anesthetic concentration. Stullken et al. increased halothane by 0.05% end-expired every 5 minutes. This probably does not allow time for alveoli–brain equilibration of anesthetic. Additionally, Stullken et al. used a continuous succinylcholine infusion. Intravenous boluses of succinylcholine have been shown to temporarily induce EEG arousal in halothane-anesthetized humans. Whether a continuous infusion of succinylcholine will produce prolonged EEG arousal is unknown. These factors would tend to produce an EEG pattern of lesser anesthetic depth than would be predicted by exhaled halothane concentrations. However, their observation of the interface of “shifting” and “anesthetic” EEG patterns at 0.63 ± 0.03% halothane is not greatly different from our observation of the stable, “anesthetic” pattern at 0.69% ± 0.03% halothane. Any differences between their observations and ours due to hysteresis, if present, are probably small.

In Groups A and B, hyperventilation and auditory stimulation failed to elicit seizure activity. This would be expected in Group A, since audiogenic seizures do not occur with halothane and pancuronium appears to augment halothane anesthesia. That atracurium produced EEG arousal in one Group B dog without eliciting audiogenic seizures probably reflects the modest level of central nervous system (CNS) stimulation caused by the doses of atracurium used in this study. However, one cannot rule out the possibility that atracurium and auditory stimulation during hypocapnia excite the CNS by differing mechanisms and are not synergistic.

In summary, pancuronium had no apparent effects on CMRO₂, CBF, ICP, or EEG at anesthetic concentrations of halothane. At sub-MAC halothane concentrations, atracurium consistently produced EEG evidence of delayed cerebral arousal; however, arousal did not result in significant increases in CMRO₂, CBF, or ICP. Cerebral stimulation by atracurium was largely eliminated by 1.0 MAC halothane concentrations. Neither pancuronium nor atracurium produced aberrancies in cerebral metabolites consistent with cerebral ischemia.

We conclude that in dogs any cerebral stimulation by clinically relevant doses of atracurium is modest in magnitude, is probably independent of the drug's neuromuscular blocking effects, and is assumed to be due to the metabolite laudanosine, a known cerebral stimulant.

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References