EFFECTS OF ATRACURIUM, VECURONIUM OR PANCURONIUM PRETREATMENT ON LIGNOCAIN SEIZURE THRESHOLDS IN CATS

W. L. LANIER, F. W. SHARBROUGH AND J. D. MICHENFELDER

Neuromuscular blocking drugs are large, charged molecules which do not readily cross the blood–brain barrier [1–3]; however, cerebral effects of i.v. administered depolarizing and non-depolarizing myoneural blockers have been reported. In general, when neuromuscular blocking drugs are given to lightly anaesthetized subjects, depolarizing drugs tend to produce cerebral stimulation, while non-depolarizing drugs tend to depress cerebral function. This depression of cerebral function by non-depolarizing neuromuscular blockers has been manifested as EEG synchronization following i.v. gallamine [4] and as a reduction in the minimum alveolar anaesthetic concentration (MAC) in man following i.v. pancuronium [5]. Although the cerebral effects of vecuronium are not as thoroughly defined as those of many of the other commonly used drugs, vecuronium would be expected to affect cerebral function in a manner similar to pancuronium. Both myoneural blockers produce a non-depolarizing blockade, while neither has cerebral-active metabolites or an effect on circulating histamine, all of which are proposed mechanisms whereby myoneural blocking drugs may affect cerebral function [6].

In contrast to the effects of other non-depolarizing neuromuscular blocking drugs, atracurium, when given in large i.v. doses (1.0 mg kg⁻¹) to lightly anaesthetized dogs, produces EEG arousal [6]. This arousal response has been attributed to the atracurium metabolite laudanosine [6], a known cerebral stimulant [7] and seizure-producing agent [8, 9]. It is unknown if the cerebral stimulating effects of atracurium, as demonstrated by the EEG, correlate with alterations in seizure thresholds of any origin.

Generalized seizure activity is a well appreciated complication of excessive local anaesthetic administration, including the local anaesthetic lignocaine [10]. Furthermore, neuromuscular blocking drugs may be used in many patients in whom lignocaine is used for the induction of a regional anaesthetic technique, as

SUMMARY

Among the non-depolarizing neuromuscular blocking drugs, atracurium appears to be unique in its ability to produce cerebral stimulation in lightly anaesthetized animals. This effect is attributed to the atracurium metabolite, laudanosine. The following studies were performed to determine if pretreatments with the non-depolarizing neuromuscular blockers pancuronium, atracurium or vecuronium would differ in their effects on the seizure threshold of lignocaine. Adult mongrel cats were anaesthetized with 1.0 MAC halothane in oxygen and nitrogen. Ventilation, blood-gas tensions, acid-base balance and temperature were controlled. Cats received pancuronium 0.2 mg kg⁻¹ i.v. (n = 7), atracurium 1.0 mg kg⁻¹ i.v. (n = 7) or vecuronium 0.2 mg kg⁻¹ i.v. (n = 7). Ten minutes after the administration of the myoneural blocker, all cats received lignocaine 4 mg kg⁻¹ min⁻¹ i.v. until the onset of EEG evidence of generalized seizure activity. At seizure onset, there were no statistically significant differences among the cumulative lignocaine doses or the serum lignocaine concentrations in cats pretreated with pancuronium, atracurium or vecuronium.
an i.v. general anaesthetic supplement, or as an antiarrhythmic agent. Previous studies have demonstrated that the seizure threshold of lignocaine may be altered by gallamine [11] and suxamethonium [12]. The effects of pancuronium, vecuronium and atracurium on the lignocaine seizure threshold have not been reported.

The following study was designed to test the hypothesis that, since EEG evidence of cerebral arousal following i.v. atracurium differs uniquely from the cerebral response to other non-depolarizing myoneural blocking drugs, atracurium will also differ in its effect on lignocaine-seizure thresholds when compared with pancuronium and vecuronium.

**MATERIALS AND METHODS**

Formal approval for these studies was obtained from the Institutional Animal Care and Use Committee. Subjects were 21 unmedicated mongrel cats weighing 3.7 ± 0.2 kg (mean ± SEM). Anaesthesia was induced with 3% inspired halothane in oxygen, and the trachea was intubated without the use of a neuromuscular blocking drug. Anaesthesia was maintained with 1.5% inspired halothane in 30–40% oxygen and nitrogen during the preparatory period. Ventilation was controlled with a Harvard ventilator and adjusted along with the inspired oxygen concentration to maintain control values of blood-gas tensions (Instrumentation Laboratory, Inc. electrodes at 37 °C) at $P_{O_2}$ 20.3 ± 0.3 kPa (mean ± SEM) and $P_{CO_2}$ 4.7 ± 0.0 kPa. Cannulae were placed in a femoral artery for continuous pressure measurements and blood sampling, and in femoral and forelimb veins for fluid and drug administration. During the preparatory period, cats were given i.v. infusions of lactated Ringer’s solution 10 ± 3 ml kg$^{-1}$ (two cats in each group) or 5% dextrose in lactated Ringer’s solution 7 ± 1 ml kg$^{-1}$ (five cats in each group). Sodium bicarbonate was given i.v., if needed, to maintain the buffer base (BB+) around 40 mmol litre$^{-1}$. Since the infusions of lignocaine decreased mean arterial pressure (MAP) during the study period, phenylephrine 0.04 mg ml$^{-1}$ i.v. was used in 20 of 21 cats to maintain MAP ≥ 60 mm Hg. Rectal temperature was measured with a thermistor and maintained near 38°C with heating lamps and pads. Inspired and end-expired halothane concentrations were measured with an infra-red analyser calibrated for halothane (Beckman Medical Gas Analyzer LB-2). Heart rate (HR) was determined from a lead II ECG which was continuously recorded using skin needle electrodes. A six-lead, three-channel bi-frontal, bi-parietal, and bi-occipital EEG was recorded from gold electrodes glued to the calvarium. A 10-kΩ “dummy” circuit was also recorded to detect electrical artefacts. Electroencephalographic filter settings were such that the linear frequency response range was between 1 and 70 Hz.

Fifteen minutes before the definitive study period, the halothane concentration was decreased to 0.83 ± 0.00% end-expired (1.0 MAC). The cats were then divided into three groups and, over a 1-min period, given i.v. infusions of atracurium 1.0 mg kg$^{-1}$ ($n = 7$), pancuronium 0.2 mg kg$^{-1}$ ($n = 7$), or vecuronium 0.2 mg kg$^{-1}$ ($n = 7$). These doses were chosen to represent twice the intubating dose of the various drugs in man. Ten minutes after the completion of the administration, lignocaine hydrochloride 4 mg kg$^{-1}$ min$^{-1}$ in 0.9% saline solution 3.6 ml min$^{-1}$ was infused to a forelimb vein at a Y-piece to which an additional “flush” of 0.9% saline solution was infused. The flush solution was begun at a rate of 3.6 ml min$^{-1}$ before the lignocaine infusion and continued for 30 s after the cessation of the lignocaine infusion. Assuming the pharmacokinetics of atracurium and its metabolite laudanosine are similar in cats, dogs and man [13, 14], this sequence of neuromuscular blocker followed in 10 min by lignocaine would produce near maximum increases in brain laudanosine concentration at the time of seizure onset [6].

EEG activity was recorded before and during the infusion of the myoneural blocker, and at 2.5, 5.0 and 7.5 min after the infusion; and continuously, beginning 1 min before the infusion of lignocaine until the end of the study.

Since all study subjects were paralysed, it was necessary to define seizure onset using EEG criteria. The infusion of lignocaine was discontinued with the onset of seizure activity, which was defined as the appearance of electrical attenuation in all three EEG leads ≥ 1.0 s followed by polyspike or polyspike and wave activity (fig. 1). These criteria were determined by observing the most frequent seizure pattern that was readily reproducible and easily recognized prospectively in real time as determined by pilot studies. The EEG criteria used to define the onset of seizure activity were similar to those used in previous studies [12, 15, 16].
An attempt was made to compare seizure thresholds in treated cats with those in unparalysed, placebo-treated cats; however, this was not technically possible. During the infusion of lignocaine in unparalysed cats in pilot studies, muscle twitching often preceeded EEG evidence of seizures. This phenomenon has been described previously in man [17]. The lignocaine-induced muscle twitching, along with ocular and lingual movements, produced EEG artefacts which made accurate assessment of the onset of seizure activity impossible using electrodes glued to the calvarium.

Arterial blood samples that would be used for blood-gas analysis and serum lignocaine determinations were drawn at the time of the onset of seizure activity in all cats. Samples for the measurement of serum lignocaine concentration were frozen at $-70\,^\circ\mathrm{C}$ until analysed using an enzyme immunoassay technique (EMIT: Syva Company, Palo Alto) [18]. All samples were serially diluted until dilutions were obtained which provided EMIT measurements within the 0–12-$\mu$g ml$^{-1}$ calibration standards. This methodology has a reported coefficient of variation of 3.4%, and results from this technique correlate well with values obtained by gas–liquid chromatography ($r = 0.976$) [18]. At the completion of study, cats were killed with i.v. potassium chloride, and the isoelectric EEG was evaluated for artefacts. Retrospective EEG analysis was performed by a blinded observer (F.W.S.).

Comparison of data was made using paired $t$ tests and Bonferroni’s correction of unpaired $t$ tests. $P < 0.05$ was considered significant when comparing paired data, and, because multiple comparisons were made, a Bonferroni’s corrected $P$ value of $0.05/3 = < 0.016$ was considered significant when comparing unpaired data. The correlation between the duration of the lignocaine infusion and serum lignocaine concentration was assessed by determining the Pearson product–moment correlation coefficient. Data are presented as the mean $\pm$ SEM.

RESULTS

Values for physiological variables during the control period and at the onset of seizures are listed in table I. There were no significant
RELAXANTS AND LIGNOCAINE SEIZURES

TABLE I. Systemic variables (mean ± SEM) during the control period and at seizure onset. n = 7 for all groups. *Significantly different from control value (P < 0.05). There were no significant differences among study groups during either measurement period.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Seizure onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atracurium</td>
<td>Vecuronium</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>3.6 ± 0.2</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>Pa (kPa)</td>
<td>20.4 ± 0.4</td>
<td>20.3 ± 0.5</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>4.5 ± 0.0</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>PH</td>
<td>7.38 ± 0.01</td>
<td>7.37 ± 0.02</td>
</tr>
<tr>
<td>BB⁺ (mmol litre⁻¹)</td>
<td>42 ± 0</td>
<td>41 ± 1</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>27 ± 2</td>
<td>28 ± 1</td>
</tr>
<tr>
<td>Rectal temp. (°C)</td>
<td>37.9 ± 0.1</td>
<td>38.0 ± 0.1</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>121 ± 5</td>
<td>129 ± 8</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>186 ± 14</td>
<td>174 ± 17</td>
</tr>
<tr>
<td>Expired halothane (%)</td>
<td>0.83 ± 0.00</td>
<td>0.83 ± 0.00</td>
</tr>
<tr>
<td>Serum lignocaine (µg ml⁻¹)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of lignocaine infusion (s)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cumulative lignocaine dose (mg kg⁻¹)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Differences among groups at either measurement period. Infusion of the various neuromuscular blocking drugs during 1.0 MAC halothane anaesthesia had no apparent independent effect on the EEG.

At seizure onset, several variables had changed from control values by quantities that were physiologically acceptable but statistically significant. Mean arterial pressure and HR tended to decrease in all groups; however, the changes in MAP were significant only in pancuronium- and vecuronium-treated cats, while the decreases in HR were significantly different only in atracurium- and pancuronium-treated cats. A decrease in BB⁺ of 2 mmol litre⁻¹ in atracurium-treated cats and a mean decrease in temperature of 0.2 °C in vecuronium-treated cats were both statistically significant.

Serum lignocaine concentrations obtained at the onset of seizure activity did not significantly differ among groups of cats pretreated with atracurium 42.1 ± 4.8 µg ml⁻¹, pancuronium 68.2 ± 11.6 µg ml⁻¹ or vecuronium 47.6 ± 5.2 µg ml⁻¹. The mean cumulative lignocaine dose at the onset of seizure activity for all cats was 17.3 ± 0.8 mg kg⁻¹ and did not significantly differ among the groups (table I). There were no significant differences among the groups regarding the durations of lignocaine infusions (table I), and there was no meaningful correlation between the durations of the infusions of lignocaine and measured serum lignocaine concentrations (r = -0.03, P > 0.8) (fig. 2). Mean phenylephrine dose for all cats was 0.16 ± 0.04 mg and did not significantly differ among groups.

FIG. 2. The relationship between the durations of the lignocaine infusion and serum lignocaine concentrations. There was no meaningful correlation between the durations of lignocaine infusions—and thus cumulative lignocaine doses—and the measured serum lignocaine concentrations (r = -0.03; P > 0.8). • = Atracurium; ○ = pancuronium; □ = vecuronium.

DISCUSSION

Neuromuscular blocking drugs are large charged molecules that are reported either not to cross the blood–brain barrier [2, 3] or to cross the blood–
The afferentation theory of cerebral arousal probably best explains previous reports of the influence of gallamine and suxamethonium on lignocaine seizures. Gallamine has no known effect on cerebral blood flow, yet gallamine-induced non-depolarizing neuromuscular blockade increases the lignocaine seizure threshold in monkeys [11]. We must assume that the gallamine-induced alterations in seizure threshold are the result of some functional interaction between lignocaine and gallamine-induced cerebral electrical depression [4]. In contrast to the increase in lignocaine seizure threshold produced by gallamine, suxamethonium-induced depolarizing neuromuscular blockade decreases the lignocaine seizure threshold in cats [12]. It is unclear whether this effect is the result of a functional interaction between suxamethonium and lignocaine, or whether the seizure threshold decrease was the result of an increase in cerebral blood flow following suxamethonium [21]. All three blocking drugs used in the current study produced complete non-depolarizing neuromuscular blockade, and their effects on cerebral function, as predicted by the afferentation theory, should not differ.

Contrary to the cerebral effects of non-depolarizing drugs predicted by the afferentation theory, atracurium in large doses (1.0 mg kg\(^{-1}\)) produced EEG arousal in dogs receiving sub-MAC concentrations of halothane [6]. This arousal response has been attributed to the metabolite laudanosine, a known cerebral stimulant [7] and seizure-producing agent [8, 9]. Although the production of laudanosine by clinical doses of atracurium is much less than the laudanosine doses previously reported to produce seizures in animals [6], we hypothesized that the atracurium-induced production of laudanosine might be sufficient to alter the lignocaine seizure threshold. The current data do not support that hypothesis.

The release of histamine induced by certain myoneural blockers may also affect cerebral function and influence the amount of lignocaine required to induce seizures. Histamine is a direct cerebral vasodilator producing increases in cerebral blood flow [22], and there is some evidence that histamine has a stimulating effect on cerebral electrical activity [23]. In addition, histamine can produce increases in \(\text{Pa}_\text{CO}_2\) secondary to an increase in pulmonary deadspace [24], and increases in \(\text{Pa}_\text{CO}_2\) can in turn produce increases in cerebral blood flow [25] and cerebral electrical excitation [26]. Atracurium is reported to release histamine in approximately one-third the amount noted following the administration of tubocurarine [27], while pancuronium and vecuronium do not readily release histamine [28, 29]. Despite histamine release after atracurium, we recently demonstrated no significant alterations in CBF in dogs given massive doses of either atracurium or pancuronium during 1.0 MAC halothane anaesthesia [6]. There were no significant alterations in \(\text{Pa}_\text{CO}_2\) during the present study, so we can discount histamine-induced carbon dioxide-mediated cerebral effects following atracurium; however, our study design would not eliminate any direct histamine-induced effects on either CBF or cerebral electrical activity.

In the present study, we elected to administer lignocaine as a continuous infusion until the onset of seizures, as has previously been reported [11, 17, 30]. Since lignocaine acts as a general anaesthetic at subconvulsant doses [31], this
methodology resulted in an initial synchronization of the EEG as has previously been reported [30], followed by the onset of isolated spikes that were difficult to distinguish from background activity, followed by the combination of polyspike or polyspike and wave activity and electrical attenuation. The latter was used as the seizure “marker” in this study, for it was readily identifiable in real time, was similar to the marker used in previous reports, and is reported to coincide with the onset of tonic–clonic muscle activity in cats [12, 15, 16, 32].

The definition of seizure threshold in previous studies using infusions of lignocaine has been described in terms of the cumulative dose of lignocaine given at the onset of seizures [17, 30] or the plasma lignocaine concentrations measured at the onset of seizure activity [11]. In the present study, we measured both serum lignocaine concentrations and cumulative lignocaine doses. There were no significant differences between the groups in the seizure threshold in our study, regardless of the criteria used to define seizures. In addition, we found no correlation between the cumulative dose of lignocaine and the measured serum lignocaine concentrations, suggesting that these measurements of lignocaine seizure thresholds cannot be used interchangeably.

The fact that no difference was noted in the lignocaine seizure threshold after pretreatment with atracurium v. vecuronium and pancuronium may be attributable to a number of factors. First, the production of laudanosine by the doses of atracurium used may have been insufficient to produce a change in seizure threshold [6]. Second, histamine release following atracurium may have been insufficient to alter cerebral function meaningfully, or the cerebral effects of histamine may have been negated by controlling PaCO₂. Third, the reported cerebral effects of the neuromuscular blockers studied [5, 6] may affect the brain by mechanisms which are independent of the mechanisms by which lignocaine alters cerebral function.

In summary, we could find no difference in lignocaine seizure thresholds among groups of halothane-anaesthetized cats pretreated with atracurium, vecuronium or pancuronium. Assuming our data in cats are transferable to man, we conclude that intubating doses of the three drugs studied can be interchangeably administered in patients also receiving lignocaine without increasing the relative risk of lignocaine-induced convulsions.

ACKNOWLEDGEMENTS

This research was supported in part by Research Grant NS-07507 from the National Institutes of Health, United States Public Health Service.

The authors would like to thank Thomas P. Moyer Ph.D., and William J. Gallagher for their technical assistance in performing these studies.

REFERENCES


