MODIFICATION OF CENTRAL NERVOUS SYSTEM EFFECTS OF LAUDANOSINE BY INHALATION ANAESTHETICS


Laudanosine, a metabolite of atracurium, produces seizures in rabbits when administered in a bolus dose of 3.0 mg kg\(^{-1}\) i.v. [1]. However, no reports of perioperative seizures or other manifestations of central nervous system (CNS) excitation in surgical patients have been reported, suggesting that general anaesthesia may "protect" the CNS from the stimulating properties of laudanosine. To examine this hypothesis, we studied the effects of different inhalation anaesthetics on the plasma concentration of laudanosine which produces purposeless, unco-ordinated movements of the entire body in rabbits.

METHODS AND RESULTS

With the approval of the University of California Committee on Animal Research, we studied 40 non-fasted, unpremedicated, male New Zealand white rabbits. Anaesthesia was induced with halothane in oxygen via a mask and the trachea was intubated without neuromuscular block. For normocapnic rabbits, ventilation was spontaneous and Pa\(_{\text{CO}_2}\) remained in the range 4.5–5.3 kPa; deviations from this range were corrected by assisting ventilation mechanically or adding inspired carbon dioxide to maintain normocapnia. Hypocapnia was induced in five rabbits by hyperventilation (Pa\(_{\text{CO}_2}\) 2.7–3.3 kPa). Rectal temperature was maintained at 39–40 °C in all animals using surface warming. A femoral artery was cannulated for blood sampling and arterial pressure measurement and an ear vein was catheterized to allow administration of laudanosine i.v. The scalp of each animal was incised and burr holes were drilled for insertion of dural electrodes which were fixed to, but isolated from, the skull with acrylic resin. A bipolar fronto-frontal electroencephalogram (EEG) was obtained via these electrodes using a Grass Model 7P5-A EEG pre-amplifier (sensitivity 150 µV cm\(^{-1}\)) and a Grass Model 7 polygraph.

Rabbits were assigned randomly to receive no
CNS EFFECTS OF LAUDANOSINE

TABLE I. Anaesthetic regimens and study results (mean (SD)). †Volatile anaesthetic concentrations are end-tidal values in oxygen. * Significantly different from group 1 (P < 0.05)

<table>
<thead>
<tr>
<th>Group (n = 5)</th>
<th>Anaesthetic regimen†</th>
<th>CNS excitation concentration of laudanosine (ETPC) (µg ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No anaesthesia</td>
<td>5.0 (0.9)</td>
</tr>
<tr>
<td>2</td>
<td>2.0% Enflurane</td>
<td>9.1 (1.4)*</td>
</tr>
<tr>
<td>3</td>
<td>1.0% Halothane</td>
<td>11.8 (2.5)*</td>
</tr>
<tr>
<td>4</td>
<td>1.6% Isoflurane</td>
<td>11.3 (2.8)*</td>
</tr>
<tr>
<td>5</td>
<td>2.0% Enflurane with hypocapnia</td>
<td>9.8 (1.6)*</td>
</tr>
<tr>
<td>6</td>
<td>70% Nitrous oxide</td>
<td>3.9 (1.3)</td>
</tr>
<tr>
<td>7</td>
<td>1.0% Halothane with 70% nitrous oxide</td>
<td>6.7 (1.2)</td>
</tr>
<tr>
<td>8</td>
<td>0.7% Halothane</td>
<td>12.3 (1.5)*</td>
</tr>
</tbody>
</table>

anaesthesia (control) or one of seven anaesthetic regimens (table I) (n = 5 for each group). We examined the effects of different volatile anaesthetics (equipotent end-tidal concentrations of halothane, isoflurane and enflurane, measured by gas chromatography), the effects of differences in depth of anaesthesia (1.0% v. 0.7% halothane), the influence of hyperventilation (enflurane in the presence and absence of hypocapnia), and of 70% nitrous oxide (alone and in combination with 1.0% halothane). Each regimen was maintained for a minimum of 2 h, at which time laudanosine was administered by infusion pump (AVI 100 Volumetric) at a rate of 0.5 mg kg⁻¹ min⁻¹ until the onset of CNS excitation. Excitation was defined as purposeless, unco-ordinated movements of the entire body. In the control group, tracheal tubes were removed following attachment of monitors and the animals were allowed to recover from halothane anaesthesia for 2 h. During infusion of laudanosine, animals were placed in a small cage but not restrained.

Heparinized arterial blood samples were obtained before each study and immediately after CNS excitation was observed, in order to determine the CNS excitation-threshold plasma concentration (ETPC) of laudanosine. Plasma concentrations of laudanosine were measured by liquid chromatography sensitive to laudanosine 10 ng/ml of plasma.

The mean ETPC value for each group was compared with control by analysis of variance and Dunnett’s test. Other inter-group comparisons were made by analysis of variance and Student–Newman–Keuls multiple-range test. We assumed differences were statistically significant when P < 0.05.

The mean ETPC of laudanosine increased significantly from control in all groups except those given nitrous oxide (groups 6 and 7) (table I). Nitrous oxide alone did not influence ETPC, but the addition of nitrous oxide to 1.0% halothane decreased significantly the ETPC of laudanosine to less than the value obtained for 1.0% halothane alone (6.7 v. 11.8 µg ml⁻¹). Decreased depth of anaesthesia (groups 3 v. 8) and hypocapnia (groups 2 v. 5) did not alter ETPC significantly.

COMMENT

We found that, during halothane anaesthesia, plasma concentrations of laudanosine of 8.6–14.6 µg ml⁻¹ resulted in CNS excitation. These values are similar to those obtained for other species anaesthetized with halothane. For example, Ingram and colleagues observed changes in the EEG of cats associated with blood concentrations of laudanosine 7.9 (1.7) µg ml⁻¹ [2]. Chappie and colleagues found that concentrations of laudanosine greater than 14 µg ml⁻¹ produced EEG polyspikes and paroxysmal bursts followed by myoclonic jerks and facial twitches in dogs, and that clonic seizure activity occurred at plasma concentrations of laudanosine exceeding 17 µg ml⁻¹ [3].

Our study was designed initially to determine the effects of volatile anaesthetics on the plasma concentration of laudanosine required to produce grand mal seizure EEG changes. However, in 75% of the animals studied, motor manifestation of profound CNS excitation was not associated with this type of EEG changes. Thus our study represents an investigation of the effects of laudanosine on motor manifestations of CNS excitation, but the results are similar to the studies above in which the EEG was used as an index of excitation.

In this study, the plasma concentration of laudanosine that resulted in CNS excitation was greater in the presence of volatile anaesthetics. Our data suggest that halothane anaesthesia “protects” rabbits from the CNS-stimulating properties of laudanosine. The plasma concentrations of laudanosine that produced CNS excitation in our awake animals (5.0 (0.9) µg ml⁻¹) and in those receiving 70% nitrous oxide (3.9 (1.3) µg ml⁻¹) were similar to the peak plasma...
concentrations of laudanosine (1.9–5.1 μg ml⁻¹) found by Yate and colleagues [4] in unanaesthetized intensive care patients receiving infusions of atracurium 0.6–0.9 mg kg⁻¹ h⁻¹ for 38–219 h to facilitate mechanical ventilation. Although Yate and co-workers observed no evidence of CNS excitation, these patients were maintained under conditions which would have made it difficult to detect laudanosine-induced CNS activity. Patients were paralysed and sedated with midazolam, which may increase the ETPC for laudanosine, and EEG was not monitored.

The rabbits anaesthetized with nitrous oxide did not exhibit the increase in the ETPC of laudanosine observed in animals given volatile anaesthetics. The effects of nitrous oxide on ETPC may differ from those of volatile anaesthetics because of differences in anaesthetic depth, although decreasing depth of anaesthesia (groups 3 v. 8) did not alter ETPC. It is possible that nitrous oxide itself may produce CNS excitation, enhancing that of laudanosine, and there is some theoretical evidence that nitrous oxide and laudanosine exert CNS effects via an action at opioid receptors [5, 6]. This may explain how nitrous oxide and laudanosine interact to eliminate the “protective” effect of halothane.

In conclusion, our study has shown that the volatile anaesthetics increased the CNS excitation-threshold plasma concentration of laudanosine in rabbits. Such an interaction may occur also in surgical patients given volatile anaesthetics and atracurium. In contrast, nitrous oxide provided no “protective” effect and antagonized the protective effect of halothane in rabbits.

ACKNOWLEDGEMENTS

Supported in part by the National Institutes of Health (GMR01–26403–07) and the Anesthesia-Pharmacology Research Foundation.

We are grateful to Ayerst Laboratories for donating halothane (Fluothane), and Anaquest Ltd for donating enflurane (Ethrane) and isoflurane (Forane).

REFERENCES