LACK OF CORRELATION BETWEEN THE ANAESTHETIC AND ANTI-CONVULSANT POTENCIES OF ALTHESIN, KETAMINE AND METHOHEXITONE

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The convulsant/anti-convulsant properties of different anaesthetics are of clinical importance and of mechanistic interest. For example, much has been written for and against the use of Althesin, ketamine and methohexitone in patients with status epilepticus [1–3]. However, less is known about anaesthetic interactions with chemically-induced convulsions, and there have been relatively few systematic comparative studies. Certain anaesthetics are known to provide good protection against hyperbaric convulsions [4], but little is known about the basis of these effects.

In the present study the two chemical convulsants selected were bicuculline and strychnine: bicuculline is a γ-aminobutyric acid (GABA) receptor antagonist thought to act directly on one of the types of GABA receptors; strychnine blocks the inhibitory action of glycine at postsynaptic receptors in the spinal cord and the (antagonizing) feedback inhibition by Renshaw cells on α-motor neurones. Althesin, ketamine and methohexitone were selected as the anaesthetics for this study because their interactions with hyperbaric-induced convulsions had been investigated previously [5, 6], and because they were representative of the different types of i.v. agents. Some of the anti-convulsant effects of the inhalation anaesthetics have been documented [7]; results suggest that halothane and enflurane have a protective effect against convulsions associated with reduced GABAergic transmission.

The present study was intended to test the hypothesis that there is a correlation between the anaesthetic and anti-convulsant potencies of the i.v. agents. Evidence suggesting such an hypothesis includes the work on mice, selectively bred for resistance to nitrous oxide anaesthesia, which demonstrated that they were significantly more sensitive to strychnine and pentylenetetrazol convulsions (but not bicuculline convulsions) than those bred for susceptibility to nitrous oxide anaesthesia [8]. Evidence against the hypothesis includes the lack of correlation between the structure–activity relationships governing anaesthesia per se and those related to convulsant activity or central nervous system irritability [9]. Finally, there is no a priori reason for assuming that the anaesthetics have equal anti-convulsant potencies, even if it could be demonstrated that

SUMMARY

Using Sprague–Dawley rats, the anti-convulsant potencies of Althesin, ketamine and methohexitone were determined for bicuculline- and strychnine-induced seizures and compared with their effects on hyperbaric seizures. All three anaesthetics protected against both types of chemical convulsants; the degree of protection varied from 34 to 151%, with Althesin being the most effective. However, there was no correlation between their anti-convulsant and anaesthetic potencies, and no relationship between the effects on chemical convulsions and the interactions of the same agents with hyperbaric convulsions. These data suggest that the order of anti-convulsant potencies at equivalent anaesthetic concentration is Althesin > ketamine = methohexitone, and that neither bicuculline- nor strychnine-induced seizures are a good model for hyperbaric convulsions.
that pharmacological property for a particular agent was closely related to its anaesthetic action. These experiments were designed to study any relationship between anaesthetic and anti-convulsant potency.

**MATERIALS AND METHODS**

A total of 44 female Sprague–Dawley rats (mean weight 245 g, SD 35) were used. These were supplied from a specified pathogen-free breeding unit; the corresponding age range was 8–12 weeks (young adults). A 24-gauge “Abbocath” was inserted to the lateral tail vein under 1% halothane in oxygen anaesthesia and was taped securely in place. A double-lumen catheter was connected to the Abbocath to permit simultaneous infusion of both anaesthetic and convulsant.

Three i.v. anaesthetics were studied: Althesin (alphaxalone/alphadolone acetate in Cremophor EL; Glaxo Ltd); ketamine (Ketalar; Parke Davis Ltd) and methohexitone sodium (Brietal; Lilly & Co. Ltd). The anaesthetic was infused from a small infusion pump (MS 16, Graseby Dynamics Ltd) and each rat was maintained at a constant infusion rate for a minimum of 15 min to ensure that the anaesthetic depth was stable. Anaesthesia was assessed in terms of a moderate abdominal twitch response to a 10-V electrical stimulus applied to a tail. The infusion rate was varied in each animal until this response was just prevented.

The temperature of the anaesthetized rats was measured with a rectal thermistor probe and maintained at 37 ± 1 °C with a heating mat.

Bicuculline (Sigma) was dissolved in hydrochloric acid 0.1 mol litre⁻¹ and titrated back to pH 3.0 with sodium hydroxide 10 mol litre⁻¹. A stock solution of 1 mg ml⁻¹ was prepared and frozen in 1-ml aliquots. It was diluted immediately before use with 0.9% saline to give a final concentration of 0.1 mg ml⁻¹. Strychnine (Sigma) was dissolved in distilled water to give a stock solution of 25 mg ml⁻¹. This was frozen in 1-ml aliquots and diluted with saline on the day of the experiment to give a final concentration of 2.5 mg ml⁻¹.

After 15 min of anaesthesia, either bicuculline or strychnine was infused via a Braun “perfusor” pump (rate of infusion 1.62–1.67 ml min⁻¹). The time taken to reach the end-point was recorded; for bicuculline this was the first myoclonic jerk, as full seizures did not always occur in the presence of Althesin. For strychnine, the end-point used was the first full convulsion, as this was the first unambiguous sign of the desired effect of the drug.

Control animals received convulsant alone. They were placed in a small restraining cage, and a minimum of 15 min was allowed for recovery from the insertion of the catheter before the convulsant was infused. Each rat was used once and, when the convulsant end-point was reached, was rapidly killed with an overdose of Althesin. Both pumps were accurately calibrated after each experiment. Results were calculated as mg kg⁻¹ of convulsant required. All statistical comparisons used the Mann-Whitney *U*-test, to avoid any assumptions about the distribution of the data.

**RESULTS**

The anaesthetic potencies were measured as the minimum infusion rates necessary to achieve anaesthesia in the individual animals. These data were then combined for each anaesthetic group to determine the mean infusion rates (±SEM) which were as follows: Althesin (total steroid content) 0.607 (±0.010) mg kg⁻¹ min⁻¹, *n* = 11; ketamine 2.08 (±0.015) mg kg⁻¹ min⁻¹, *n* = 11; and methohexitone 1.10 (±0.024) mg kg⁻¹ min⁻¹, *n* = 10.

The convulsant doses of either bicuculline or strychnine were measured either in control animals or in anaesthetized animals and then combined to estimate the mean amount of convulsant required in each group (preliminary experiments demonstrated that the vehicle for Althesin (Cremophor EL) had no effect on the convulsant end-point). These data, together with the statistical comparisons between the means, are presented in table I. The anti-convulsant potencies, at equivalent anaesthetic concentrations, were calculated

**Table I. The amount of bicuculline or strychnine required (mg kg⁻¹) for the convulsion end-point. The data were compared with the Mann–Whitney *U*-test. ***P < 0.005, **P < 0.01, *P < 0.05**

<table>
<thead>
<tr>
<th>Convulsant</th>
<th>Control</th>
<th>Althesin</th>
<th>Ketamine</th>
<th>Methohexitone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicuculline</td>
<td>Mean</td>
<td>0.505</td>
<td>1.28***</td>
<td>0.665**</td>
</tr>
<tr>
<td></td>
<td>SEM</td>
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<td>0.17</td>
<td>0.02</td>
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<tr>
<td></td>
<td><em>n</em></td>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Strychnine</td>
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<td>2.60**</td>
<td>1.48*</td>
</tr>
<tr>
<td></td>
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<td></td>
<td><em>n</em></td>
<td>4</td>
<td>6</td>
<td>6</td>
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as the percentage increase in convulsant required in the presence of anaesthetic relative to awake control data; these are shown in figure 1 (left-hand side).

The lack of correlation between anaesthetic and anti-convulsant potencies is demonstrated in figure 1; thus, despite the anaesthetics being at equivalent anaesthetizing concentrations, the degree of anti-convulsant activity was not the same. Althesin was three to four times more effective than either ketamine or methohexitone in increasing the chemical convulsion thresholds ($P < 0.01$). Ketamine and methohexitone provided protection against both types of convulsion, but were not significantly different from each other for either convulsant. Figure 1 also includes data for anaesthetic protection against hyperbaric convulsions [5, 6], which is considered in the Discussion section.

**DISCUSSION**

The mean anaesthetizing infusion rates were in agreement with those determined in previous studies [10]. The relationships between infusion rate and plasma or tissue concentration depend on the different pharmacokinetics of the different agents. For this reason, the present study was designed to measure the relative anti-convulsant activities at the same depth of anaesthesia—as determined by a standardized behavioural response (as distinct from a fixed plasma drug concentration). Assessment of the dose of anaesthetic required for each animal was necessary because the steep dose–response curves for the anaesthetics meant that the use of a simple fixed concentration would have resulted in inadequate anaesthesia in some animals and excessive depth of anaesthesia in others. The stimulus–response that we have used had already been demonstrated to be consistent [11] and, for these agents, corresponded to relatively deep anaesthesia. There is a difficulty that it may reflect analgesia rather than anaesthesia, but it was chosen because previous studies have demonstrated that the method is analogous to the noxious stimuli and gross muscular responses used in the assessment of clinical anaesthesia [12].

It is clear from the convulsion thresholds that

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**Fig. 1.** The percentage increase in either bicuculline or strychnine requirement (compared with control values) in the presence of Althesin (ALTH), ketamine (KET) or methohexitone (MHX). For comparison the interactions of the same agents with high pressure convulsions are also plotted in terms of the percentage change in convulsion pressures relative to control values. (Hyperbaric data from Green, Halsey and Wardley-Smith [5].)
the three anaesthetics did not possess equal anti-convulsant potency against the different types of convulsion studied. Althesin, ketamine and methohexitone with hyperbaric convulsions [5, 6] have been included in figure 1, plotted in terms of the percentage increase in convulsion threshold pressures in the anaesthetized animal. The data on the hyperbaric and chemical convulsions are not directly comparable because the rats, although of the same strain, came from different populations. Nevertheless, the relative effectiveness of the three anaesthetics on each type of convulsion indicates a totally different pattern for hyperbaric convulsions (fig. 1). Both Althesin and ketamine increased the pressures at which convulsions occurred above the maximum working pressure of the hyperbaric chamber (100 ATA). In contrast, methohexitone actually reduced the threshold pressure to 60% of the control value. These data are not what would have been expected from the apparent additivity of strychnine and hyperbaric convulsions [13].

The mechanism whereby Althesin shows a greater effect than ketamine or methohexitone against bicuculline and strychnine convulsions is not clear. It is also not clear why, when ketamine and methohexitone are approximately equally effective against bicuculline and strychnine, they should have such different actions at high pressure. Althesin may act by enhancing GABAergic or glycineric inhibitory transmission or both types, since it was equally effective against both bicuculline and strychnine. Potentiation of the effects of GABA has been demonstrated [14]. It has also been shown to protect against other types of convulsion, such as hyperbaric oxygen convulsions [1] which are thought to result from disordered GABA metabolism [15]. Althesin also protects against focal epileptic discharges produced by the topical application of penicillin G [1], a GABA receptor antagonist. However, the pro-

found anti-convulsant activity of Althesin is unlikely to depend wholly on its action on GABA, since both ketamine and methohexitone are thought to have significant effects on GABA transmission.

The relative ineffectiveness of ketamine as an anti-convulsant is consistent with previous studies. Thus ketamine failed to lower the minimum electroshock seizure threshold in mice [16], and there was only an insignificant effect of ketamine on strychnine-induced seizures in mice [17]. In neurochemical studies it has been shown that ketamine potentiated the effects of GABA at its receptor site [18]. Accumulation of GABA in the synaptic cleft has been proposed as a possible mechanism of action for the anaesthetic/anti-convulsant properties of ketamine [19].

Enhancement of GABA-mediated post-synaptic inhibition has been proposed as a mechanism, at least in part, for barbiturate anaesthesia [20]. It has also been shown that pentobarbitone and thiopentone reversed the antagonistic effects of bicuculline and strychnine on GABA- and glycine-mediated inhibition, respectively [21].

The interactions of these anaesthetics with convulsants may also involve an effect on excitatory neurotransmission. Ketamine has been shown to reduce selectively excitation produced in central mammalian neurones by N-methylaspartate (NMA) [22]. With the same preparation (cat spinal neurones), methohexitone was found to have no effect on excitation produced by NMA; however, it enhanced GABA- but not glycine-mediated inhibition [23]. It is possible that this effect on excitatory neurotransmitters could partially explain the considerable differences seen between the actions of anaesthetics on hyperbaric convulsions; it has been shown that antagonists of excitatory amino acid neurotransmitters provide good protection against the HPNS [24, 25].

In addition to the differential effects of the anaesthetics, the three types of convulsions (as observed in control animals by ourselves and others) have different behavioural characteristics. Bicuculline causes myoclonic jerking followed by clonic convulsions. Tonic seizures have rarely been reported and only with high (lethal) doses. Strychnine convulsions are characterized by a tonic extension of the body and of all limbs—little or no clonic activity has been observed [26]. The classical description of a strychnine convulsion includes the tonic extension being preceded (and followed during the phase of postictal depression)
by phasic symmetrical extensor thrusts that may be initiated by any modality of sensory stimulus [27]. There is no evidence of tremor preceding strychnine-induced convulsions even when subconvulsive doses are used [28]. In contrast with these chemical convulsants, hyperbaric convulsions have very different characteristics. In rats the convulsions are either a combined clonic-tonic type, or just clonic. They are preceded at lower pressures by tremor and myoclonus.

In conclusion, there is no correlation between the anaesthetic and anti-convulsant potencies of Althesin, ketamine and methohexitone. This lack of correlation applies both to bicuculline- and strychnine-induced seizures and is in agreement with the previous study on hyperbaric convulsions. These results suggest that:

(1) The differences that we have shown in the anti-convulsant potencies of these agents suggest that care should be taken when selecting an anaesthetic for patients with seizure disorders. The present data indicate that the anti-convulsant potential under equivalent anaesthetic conditions is Althesin > ketamine = methohexitone.

(2) The three anaesthetics have differences between them in their neurochemical actions on both the GABAergic and glycinergic systems, which may contribute to their different anti-convulsant actions.

(3) Neither the bicuculline- nor the strychnine-induced seizure is an adequate model for hyperbaric-induced convulsions.

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