CENTRAL NERVOUS SYSTEM EFFECTS OF ALTHESIN (CT 1341): A NEW STEROID ANAESTHETIC AGENT

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INTRODUCTION

ALTHESIN, formerly called CT 1341, is a new non-barbiturate intravenous anaesthetic with a rapid onset and short duration of action. It is a mixture of two pregnandione derivatives and in clinical reports is frequently compared with another steroid, hydroxydione (Viadril). The pharmacologic properties of CT 1341 were investigated and reported in experimental animals by Child *et al.*¹ and subsequently in several clinical trials.²⁻¹² Only one of these reports⁹ included a brief description of its effects on the EEG of patients during surgery. Since we know of no other neurophysiological studies the present study was done to supply these data. As in previous investigations,¹³ spontaneous activity of various structures representative of the three principal systems considered of importance to the anaesthetic state was observed in chronic preparations and evoked potentials elicited by peripheral somatic stimulation were recorded in acute experiments. The techniques used will be summarized briefly since they have been described in detail in previous reports.^{13,14}

CHRONIC PREPARATIONS

METHODS

Stereotaxic implantation of bipolar electrodes into deep structures and placement of cortical electrodes was performed in five cats under pentobarbital anaesthesia at least two weeks before the first experiment. Continuous tracings from wakefulness, through induction, to onset and maintenance of analgesia, and subsequent recovery were obtained from the following structures: frontal and parietal cortex, n. ventralis postero-lateralis (VPL) representing the specific sensory system, n. amygdalae and formatio hippocampalis representing the limbic system, n. centrum medianum (C.M.) and the reticular formation (R.F.), representing the non-specific sensory system. In addition the caudatum was also implanted, because it seems to be susceptible to the effects of intravenous anaesthetics.¹⁵

End-tidal carbon dioxide was monitored by a Beckman analyzer and recorded simultaneously with the brain activity. Each ml of the commercially available solution contains 9 mg of 3 α -hydroxy-5 α -pregnane-11, 20-dione and 3 mg of 21-

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FIGURE 1. Spontaneous activity in the brain during induction of anaesthesia with CT 1341 (Althesin). Abbreviations: CTX = cortex, VPL = n. ventralis posterolateralis, Caud. = n. caudatus, Amyg. = n. amygdalae, Hipp. = formatio hippocampalis, R.F. = midbrain reticular formation, C.M. = n. centrum medianum.

A. Control tracing; the animal is alert and moving freely. Alternately increasing and decreasing amplitude in the cortex, forming a type of spindles is frequently seen in awake, alert cats. Note difference in time scale: one second against two seconds in all others.

B. Shortly after first dose (1.2 mg/kg) was given. Note spindles in subcortical structures of the sensory system, channels 2, 3, 6, and 7 and high voltage spikes particularly in the hippocampus.

C. Following total dose of 2.4 mg/kg. Note transition from spindles to hypersynchrony in VPL, C.M. and caudate nuclei, the amplitude in n. amygdalae has increased to such an extent that the gain had to be adjusted. Note calibration bar 0.2 mV, while in the others 0.1 mV.

D. Total dose 3.6 mg/kg given; note lack of burst suppression in VPL, CM, RF and caudate.

acetoxy-3 α -hydroxy-5 α -pregnane-11,20-dione dissolved in Cremophor EL. It was diluted 1:10 in normal saline to assure slow administration and accurate measurement of dosage.

RESULTS

In most animals the first dose (1.2 mg/kg) induced slowing of frequency from 35 Hz to 12–14 Hz with increased amplitude first in the VPL and caudate nuclei, followed rapidly in the other structures, the two limbic structures being usually the last affected (Figure 1B). Onset of these alterations could be observed before the injection was completed, in what is estimated as a circulation time from the site of injection to the brain. The amplitude in the sensory structures frequently alternately decreased and increased, forming spindles, somewhat com-

parable to barbiturate sleep spindles. The animals were awake and vigorously resisted restraint.

The second dose of 1.2 mg/kg was usually given only one minute after completion of the first injection because it produced no behavioural effects and because the drug induced EEG patterns were transient. There was usually no further increase in frequency but the amplitude continued to increase. The spindles in the sensory systems were interspersed with high voltage spikes and 4 to 6 Hz spikes, separated by low voltage faster activity were more and more prevalent in the limbic structures (Figure 1C). A similar pattern could be seen in the cortex of two cats, in which "sleep spindles" were frequently present during wakefulness. It should be noted, that this phenomenon is not unusual for cats (Figure 1A).

Behaviourally, after the second dose (total dose = 2.4 mg/kg), the animals were usually quiet, but withdrew the paw if pinched.

The third dose of 1.2 mg/kg (total dose = 3.6 mg/kg) was usually given 1 to 2 minutes after completion of the second injection. The patterns described above were present in all leads but tended to regress if further administration of the agent was delayed. The amplitude of the activity in VPL, C.M. and caudate decreased without changes in frequency. The 4 to 6 Hz spikes in the limbic structures, which previously were more or less continuous, occurred in bursts of 2 to 4 seconds duration separated by brief isoelectric periods (Figure 1D). They were never followed by a slow, dome like wave, but rather by low voltage fast activity.

At this time the cats did not respond to a painful stimulus, i.e. pinching of the hind paw, which we define as state of analgesia.

If Althesin was given slowly in one 3.6 mg/kg bolus, the transition from spindles to hypersynchrony and spiking was faster and, once stabilized, the patterns persisted considerably longer. In three experiments the cats became unresponsive to pain with a lower dose (2.4 to 2.8 mg/kg) and the EEG did not progress beyond hypersynchrony (Figures 1C and 2A). This pattern persisted for 8 to 10 minutes. To maintain anaesthesia for periods beyond induction (30 minutes), additional fractional doses (0.6 mg/kg) were necessary. The EEG patterns continued hypersynchronous (Figure 2A). In another three experiments the total dose (3.6 mg/kg) was needed for analgesia and the groups of high voltage spikes (as described above for the slow induction) were again seen, but persisted considerably longer before regressing to hypersynchrony. In one instance no additional administration of Althesin was necessary and analgesia concomitant with hypersynchrony (Figure 2A) persisted for 34 minutes.

Regardless of whether Althesin was given in a bolus or in fractional doses and regardless of the final total dose at the end of each experiment the animals remained unresponsive to pain even while the hypersynchrony was slowly regressing towards control patterns and although the cats appeared to be awake.

All animals were observed in the laboratory for the remainder of the day and EEG records were taken at one-, two- (Figure 2B), and four-hour intervals. The animals were also tested 24 and 48 hours and four days after the experiments and no residual effects were found in the EEG.

During induction, the cats were frequently hiccupping, coughing, yawning, licking and salivating. Fifty per cent of the animals exhibited slow, jerky head and

FIGURE 2. Spontaneous brain activity during maintenance of anaesthesia with CT 1341 (A) and during recovery (B). Same abbreviations as in Figure 1.

limb movements. Two appeared to be nauseated. There was no respiratory depression or airway obstruction. The pupils were never dilated.

ACUTE EXPERIMENTS

METHODS

Ten cats of either sex and of average weight 3.6 kg were utilized. Tracheostomy and cannulation of the femoral vessels for direct blood pressure monitoring and drug administration were performed under halothane anaesthesia. The remainder

of the operative procedures were performed using local infiltration while the cats were immobilized by fractional doses of gallamine. A monopolar electrode was placed over the sensory-motor cortex with a reference electrode over the frontal sinus. Bipolar co-axial electrodes were introduced stereotaxically into the reticular formation, n. centrum medianum and ventralis postero-lateralis. Needle electrodes for peripheral stimulation and for ECG recording were placed in both forepaws. All electrodes (stimulating and recording) were stainless steel.

Responses evoked by peripheral stimulation (8V, 0.3 msec q 2 to 6 sec) were amplified and photographed from an oscilloscope. In some experiments 20 responses were averaged on a Computer of Average Transients (Technical Measurement Corp.). The control records were obtained not less than two hours after operative anaesthesia was terminated, when all effects of the inhalation anaesthetic were expected to be eliminated.

Althesin was given intravenously either in the same fractional dosage as in chronic experiments (i.e. 1.2 mg/kg totaling 3.6 or 4.8 mg/kg), or, in a few instances, in increasing doses from 1.2 mg, 2.4, 3.6 and 4.8 mg/kg separated by 30- to 45-minute intervals as necessary.

End-tidal CO₂, blood pressure, ECG, and EEG were continuously monitored before, during, and after administration of Althesin. Evoked responses were recorded until their appearance was similar to pre-drug controls. When the study was completed, the cats were given an overdose of pentobarbital, perfused with formalin, and the brains were subsequently examined for verification of electrode placement.

RESULTS

A. *Non-specific sensory structures*

1. Midbrain reticular formation (R.F.) (Figure 3 right).

In a few experiments, responses evoked by stimulation of ipsi and/or contralateral forepaw did not change in amplitude nor in latency. In the majority of experiments, however, the amplitude was reduced with the two smaller doses (i.e. 1.2 and 2.4 mg/kg) while the simultaneous EEG tracings exhibited sleep spindles. With larger doses (3.6 and 4.8 mg/kg), while the spontaneous cortical activity was hypersynchronous (consistent with analgesia in chronic preparations), evoked potentials in the reticular formation could not be elicited. Recovery from the effects of the drug was always complete but the time was dose dependent.

2. N. centrum medianum (C.M.) (Figure 3 left).

In some experiments evoked potentials recorded in C.M. following ipsi-lateral or contralateral forepaw stimulation were increased to about twice the original amplitude and remained so during the experiment. In about the same number of animals after the first dose (i.e. 1.2 mg/kg), the amplitude was somewhat reduced and was immediately followed by another positive (downward) deflection (Figure 3, left). With the administration of additional doses, totaling 2.4, 3.6 and 4.8 mg/kg respectively, the amplitude as well as the latency of the second wave increased. After 4.8 mg/kg the amplitude was about 400 per cent of control. The duration of the second wave also increased.

FIGURE 3. Effect of CT 1341 (Althesin) on evoked responses in non-specific sensory structures, n. centrum medianum (C.M.) and reticular formation R.F. Downward deflection marks positivity in this and subsequent figure.

B. Primary sensory structures

1. N. ventralis postero-lateralis: (VPL) (Figure 4 left).

There were no substantial changes in amplitude nor in latency or duration of the evoked response to contralateral stimulation. The long latency, slow (secondary) wave was seen only once during our experiments.

2. Sensory motor cortex (area S_1): (Figure 4 right).

In most experiments there was a small, but definite increase in the positive (downward deflection) component of the primary evoked response after the first (i.e. 1.2 mg/kg) dose. There were usually no further changes in the amplitude, except in some cases there was a considerable increase after the large dose (Figure 4, right lower corner). The slow, long latency negative wave (upward deflection in the tracing) was seen invariably in all experiments; in the majority after the first dose, in some after the additional doses.

DISCUSSION

First observations on the anaesthetic properties of steroids were reported by Selye in 1941.¹⁶ The concept of anaesthetic effect was questioned by Farson¹⁷ who confirmed strong hypnotic effect of most steroids while response to pain stimulus persisted even with large overdose. Similarly in most clinical trials which

FIGURE 4. Effect of CT 1341 (Althesin) on evoked potentials in primary somato-sensory cortex (S_1) and primary thalamic relay nucleus (VPL).

followed Laubach's introduction¹⁸ of hydroxydione as a true anaesthetic, its powerful hypnotic effect with a weak analgesic effect was stressed.¹⁹⁻²⁶

Although Althesin (CT 1341) as a steroid is closely related to hydroxydione, it differs from hydroxydione in several aspects. Induction with hydroxydione was slow and large amounts of the drug were needed. With Althesin, induction is rapid. If a single dose is administered, recovery is also rapid, because it is rapidly metabolized by the liver and eliminated from the blood stream.¹⁰ Recovery is somewhat slower with prolonged infusion or repeated fractional doses. Althesin has apparently no cumulative effects; it is not deposited in adipose tissue or elsewhere and does not reenter the circulation when administration of the drug is terminated.¹

Our results demonstrate that the effects of Althesin on the central nervous system are also not as similar to hydroxydione as was expected. Althesin appears to possess good analgesic properties, at least in cats. Shivering, involuntary movements, nausea, salivation, hiccup and other unpleasant side effects were rarely seen with hydroxydione, but appear with greater frequency after Althesin, both in clinical trials¹⁰ and in our experience.

Spontaneous EEG activity during *hydroxydione* anaesthesia was only monitored in patients during operations; consequently the reports are limited to the alterations observed in the cortex.¹⁰⁻²⁶ These reports all agreed that, while induction with hydroxydione was very pleasant, patients continued to react to a surgical stimulus even when large amounts of the agent were administered, and the EEG demonstrated long (up to 10 seconds) suppression. With Althesin, the cats

ceased to react to painful stimulation while the EEG demonstrated increased activity: high voltage relatively fast activity in the VPL and caudate nuclei and hypersynchrony and/or spikes in other structures. If at onset of analgesia this activity was interrupted by isoelectricity, the burst suppression was of brief duration (one to two seconds only, Figure 1D), as compared with the 10 second suppressions reported with hydroxydione.¹⁹ During maintenance of analgesia with Althesin, patterns of hypersynchrony dominated the records and durations of the infrequent burst suppressions were limited to one second or less (Figures 1C, 2A).

The first changes in the activity of the brain during administration of Althesin were seen in the structures of the sensory system, VPL and caudate. We have seen similar effects with most volatile agents. The first high voltage spiking was seen in the hippocampus and amygdala, both structures of the limbic system known to be particularly sensitive to seizure discharges.²⁷⁻²⁸ Our observation that EEG patterns induced by a small dose (1.2 mg/kg) were only transient would indicate that the drug is rapidly eliminated from the blood stream as reported by Child.¹

The lack of residual EEG effects of Althesin after administration was discontinued, would indicate that the drug does not reenter the circulation from the tissues where it might have been deposited.

There are only two reports of the effects of *hydroxydione* on the evoked potentials recorded in the sensory system of cats.²⁹⁻³⁰ In the comprehensive report by Denavit³⁰ a large number of non-specific areas was explored, but the midbrain reticular formation was not included.

We have given *hydroxydione* to two cats and recorded evoked potentials in the reticular formation. The latency remained unchanged and the amplitude decreased in a manner similar to the depression of evoked potentials in R.F. following Althesin. Unfortunately, with the preparation of hydroxydione available to us, the dose used by Denavit (60 to 80 mg/kg) induced only spindles: i.e. EEG patterns comparable to those described by her with just an induction dose; patterns indicating a deeper level of anaesthesia (burst suppressions) were not observed. Thus, a true comparison of the effects of Althesin and hydroxydione on evoked potentials in the R.F. could not be made.

With Althesin, the amplitude of evoked potentials in the C.M. increased in some experiments with a small dose and was increasing proportionately with additional injections of the drug. Similar changes were observed by Denavit and Albe-Fessard with hydroxydione.²⁹⁻³⁰ Denavit also reports the appearance of a second, positive, long latency wave following small doses of hydroxydione and pentobarbital. In her experiments with these two drugs, the second wave disappeared when larger doses were administered. We have also observed with Althesin a second, positive-going deflection in the C.M. after the initial evoked response was elicited. However the latency, amplitude and duration of the second wave increased with deepening levels of anaesthesia, indicating possible facilitation after the initial response in susceptible animals. This interesting phenomenon was not observed during our studies with other anaesthetic agents and is currently under investigation.

Evoked responses in the primary somatic-sensory cortex and in the primary thalamic relay nucleus (VPL) are known to resist to the effects of general anaesthetics. They remained essentially unchanged in our experiments with Althesin.

SUMMARY

As part of a systematic study of the effects of anaesthetics on the central nervous system, a newly developed, short-acting steroid intravenous agent Althesin (CT 1341) was administered to cats with electrodes chronically implanted in cortex and subcortical structures. Althesin was also studied in acute experiments where effects on evoked potentials could be determined. In chronic preparations the electrodes were stereotactically placed in selected nuclei of the sensory, limbic and thalamoreticular activating systems. Following induction, anaesthesia was maintained for 30 minutes and observations continued throughout recovery time. The first effects were observed in the structures of the sensory system and followed by the limbic system. They consisted of "sleep spindles" at first and were followed by hypersynchrony which further progressed to high voltage spiking and brief periods of isoelectricity. Onset of analgesia was heralded by hypersynchrony or spiking. Hypersynchrony persisted during maintenance of analgesia (Figures 1C, 2A).

Small doses of Althesin induced only transient changes, indicating rapid elimination of the drug from the blood stream. Lack of residual EEG effects indicates that Althesin is not deposited in the tissues and does not re-enter the blood after termination of anaesthesia.

In acute experiments, the effects of Althesin on the structures of the non-specific reticulo-thalamic system were comparable to the effects of hydroxydione, another steroid anaesthetic. There was either no change or a decrease in amplitude in the evoked potentials elicited by peripheral stimulation in the reticular formation. There was increase in amplitude of evoked responses in the n. centrum medianum. There were no changes in latency or duration of the responses in either structure. Evoked responses in the specific sensory structures, primary cortex and primary thalamic relay nucleus (VPL) were essentially unchanged.

RÉSUMÉ

A des chats pourvus en permanence d'électrodes implantées dans le cortex et dans des structures souscorticales, nous avons injecté par voie endo-veineuse un produit nouveau, un agent anesthésique stéroïde à action courte : Althesin (CT 1341); cette étude fait partie d'un travail sur les effets des anesthésiques sur le système nerveux central. Nous avons également étudié l'Althesin au cours d'expériences isolées où il était possible d'étudier ses effets sur des potentiels évoqués. Chez les chats porteurs d'électrodes, ces dernières étaient placées dans des noyaux choisis des systèmes sensoriel, limbique et thalamoréticulaire. Après l'induction, l'anesthésie était maintenue durant 30 minutes et nos observations se continuaient durant le réveil. Les premiers effets ont été observés dans les structures du système sensoriel et après, dans le système limbique. Ils ont consisté en "ondes de som-

meil" d'abord et suivis par une hypersynchronie qui a évolué vers des clochers de haut voltage et de brèves périodes d'isoélectricité. Le début de l'analgésie était annoncée par l'hypersynchronie et les clochers. L'hypersynchronie a persisté durant le maintien de l'analgésie (fig. 1C, 2A).

De petites doses d'Althesin n'ont provoqué que de courts changements, laissant croire à une élimination rapide du médicament hors du courant sanguin. L'absence d'effets résiduels sur l'EEG indique que l'Althesin n'est pas déposé dans les tissus, n'entre pas de nouveau dans le sang à la fin de l'anesthésie.

Au cours des expériences spécifiques, les effets de l'Althesin sur les structures du système réticulo-thalamique non-spécifique ressemblaient aux effets de l'hydroxydione, un autre anesthésique stéroïde. Ou il n'y avait pas de changement ou il y avait une diminution d'amplitude des potentiels provoqués élicités par la stimulation périphérique de la formation réticulée. Il y avait une augmentation dans l'amplitude des réponses provoquées dans le noyau centrum médian. Il n'y avait pas de changements dans la période de latence ou la durée des réponses dans les deux structures. Les réponses provoquées dans les structures sensorielles spécifiques, le noyau de relai primaire thalamique et cortex primaire sont demeurées essentiellement inchangées.

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