ANTICONVULSANT ACTIVITY OF ALTHESIN ON EXPERIMENTAL EPILEPSY

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SUMMARY

Anaesthetic doses of Althesin were tested in rabbits using two experimental models of epilepsy—generalized (OHP; oxygen at high pressure-induced seizure) and partial (penicillin cortical-induced seizure). Althesin in both models always produced anticonvulsant activity which was more powerful in generalized convulsions. This agent was successful in preventing and treating OHP seizures. The authors conclude that a clinical history of convulsions must not be considered a contraindication to the use of this anaesthetic which has particularly useful properties for neurosurgery.

Convulsions during steroid anaesthesia were reported by Selye (1941) who described occasional fits when he injected steroids i.p. to rats. The steroid anaesthetic agents used before Althesin were hydroxydione and GR2/146. The convulsant properties of hydroxydione were first described by Price (1962), but none were reported following GR2/146. In 1973, Uppington reported convulsions following Althesin and another case was described by Rees (1975).

It was suggested that Althesin has an action similar to hydroxydione and in epileptics may cause a pre-existing resting focus to discharge and thereby produce seizures (Uppington, 1973). It was also suggested that Althesin could be considered useful to activate e.g. patterns in epileptics (Testa, Comelli and Saia, 1977). The appearance of paroxysmal bitemporal abnormalities in e.g. traces of epileptic subjects during Althesin anaesthesia was also observed (Sramka, 1975). However, Bimar and Lepouleuf (1973) reported that Althesin greatly increases the cardiazolic threshold in cats, and Emperaire and Bimar (1973) stressed that, in small doses, this drug has a consistent anticonvulsant effect on photic epilepsy in baboons. Recently, two cases of status epilepticus which did not respond to classic drugs such as diazepam and clonazepam, were successfully treated with Althesin by Alati and others (1979). According to these authors, burst suppression could be a major factor in the anticonvulsant action of Althesin since it could break the circle of epileptic discharge leading to increased oxygen consumption.

Munari and others (1977) showed that seven other cases of status epilepticus resistant to benzodiazepines were successfully treated with an anaesthetic dose of Althesin. Therefore we administered Althesin to two models of experimental epilepsy, focal and generalized in different experimental conditions to determine whether it had any convulsant or anticonvulsant action.

MATERIALS AND METHODS

Twenty adult rabbits of either sex weighing 2–3 kg were allocated to two main groups: in the first, 10 animals were exposed to oxygen at high pressure (OHP) to obtain a generalized centrencephalic seizure, while in the second group, 10 animals underwent cortical focal convulsion using penicillin.

Group 1

The animals were anaesthetized with ether and two pairs of stainless steel electrodes aseptically implanted in the skull for e.g. recording (Fp1-Fp2, 01-02). Twenty-four hours afterwards, the right cephalic vein was cannulated with a Teflon catheter under local anaesthesia (2% lignocaine 2 ml) and 3 h later the animals were exposed to OHP in a 15-litre hyperbaric chamber which had a device for injecting a drug to the cephalic catheter of the animals. The chamber was flushed with 100% oxygen for 2 min, the outlet valve sealed and the pressure increased at a uniform rate over 2 min until a pressure of 6 atm was reached.
After 17–21 min of continuous exposure at 6 atm, the e.e.g. patterns gradually changed with a marked reduction in frequency and increase in amplitude of the waves. This is considered a preseizure activity which occurs when a convulsive seizure is imminent (Raday et al., 1975). At the exact moment when preseizure activity occurred, Althesin was injected i.v. in a single dose of 0.1 ml kg⁻¹. The total exposure at 6 atm was 60 min. Five rabbits were treated in this way. Five other rabbits had an Althesin injection of the same dose at the onset of the first paroxysmal discharge after 20–23 min of continuous OHP exposure at 6 atm. The total exposure time in this subgroup was also 60 min. In all cases, decompression was carried out over 5 min.

**Group 2**

The animals were anaesthetized with ether and one pair of stainless steel screw electrodes implanted in the frontal region (Fp1–Fp2). The next day 1 cm² on the left temporo–parietal region was exposed through a trephine hole under halothane anaesthesia and the dura was opened. E.e.g. was recorded by the screw electrodes previously attached to the skull while the electro–corticogram (e.co.g) was recorded from silver ball electrodes applied to the pia. Convulsions were produced by applying a small pledget soaked with sodium penicillin G 40 000 u. ml⁻¹ to the pia. The first spike in the cortical focus appeared 100–120 s after penicillin was applied. When the spikes reached an amplitude of more than 250 μV, Althesin was injected i.v. in a single dose of 0.1 ml kg⁻¹ to five rabbits. In the remaining five rabbits, Althesin was injected in the same dose about 20 min after the penicillin application, when the highest spike frequency was reached in the cortical focus. In all experiments, the time of injection of the Althesin was 5 s. At the end of each experiment, the animals were sacrificed with a lethal dose of pentobarbitone.

**RESULTS**

In the first five animals of group 1, Althesin was injected when the preseizure e.e.g. patterns appeared (fig. 1B); in four cases it prevented seizures despite continued exposure to OHP. In one rabbit, an electrical seizure appeared after 46 min of exposure, although the animal showed no clinical symptoms.

In the second subgroup of rabbits in group 1, Althesin was injected immediately after seizure began and in all cases stopped clinical and electrical paroxysmal signs immediately after administration (fig. 1C). Exposure at 6 atm also lasted 1 h in the second subgroup, but after Althesin, none of the OHP-exposed rabbits had convulsions or abnormal electrical activity. None of the animals showed seizure activity during the decompression period.

In the second group, Althesin was injected when the isolated spikes reached greatest amplitude. Spikes (fig. 2B) and clonic jerks of the right forelimb were stopped in all cases for at least
Seizures induced by hyperbaric oxygen appear to provide a suitable model for the study of epilepsy (Wood, 1972). There are similarities between OHP-induced seizures and human epilepsy: (i) e.e.g. patterns and signs of the two types of seizures are similar (Rucci, Giretti and La Rocca, 1967; Wood, 1972; Hanna et al., 1978); (ii) derangement of cerebral gamma amino butyric acid (GABA) metabolism occurs in OHP-induced seizures as well as in some stages of epilepsy (Wood, 1972).

Furthermore, impairment of cerebral GABA metabolism also seems to be involved in focal convulsions produced by local application of cobalt and penicillin (Mutani et al., 1977).

It would appear that a similar biochemical mechanism is involved in experimental and human epilepsy and OHP may serve as a model to evaluate potential antiepileptic agents the mode of action of which does not depend on antioxidant properties (Wood, 1972).

Our results show that Althesin protects animals exposed to OHP against seizures and also stops hyperoxic convulsions when injected at the onset of the first paroxysmal discharge. Althesin produced a rapid and prolonged anticonvulsant effect in this form of seizures. This may be explained by the following:

(a) The primary event in OHP convulsions is probably major neuronal oxidation (Wood, 1972) with reduction of brain GABA concentration a secondary event (Wood, 1972). Althesin reduces cerebral oxygen consumption by about 46% (Sari et al., 1976) and may act prophylactically by reducing oxidation.

(b) Vasoconstriction in OHP may protect against neuronal oxidation (Deutrebond and Haldane, 1921). Since Althesin produces cerebral vasoconstriction demonstrated by angiography (Laxenaire, 1975), this may augment the vasoconstrictor effect of OHP.

(c) Althesin has a greater depressant effect on the reticular activating system (RAS) than the cerebral cortex (Bimar and Lepouleuf, 1973). Since Althesin produces cerebral vasoconstriction demonstrated by angiography (Laxenaire, 1975), this may augment the vasoconstrictor effect of OHP.

6 min. In rabbits which received Althesin when the spikes reached the highest frequency, the paroxysmal epileptical activity was abolished in all cases before the end of the administration (fig. 2c). Isolated spikes appeared again following an electric silence lasting about 5 min (fig. 2d) and in a short time reached large amplitude, but high frequency bursts did not reappear.
These three factors could explain the particular efficacy of Althesin on hyperoxic seizures.

Althesin also showed an anticonvulsant action during focal convulsions. Its activity in this experimental model is constant but of short duration and is probably related to the depressant cortical action. Moreover, it produces prolonged suppression of high frequency bursts which are signs of increased cortical excitability. This suggests that Althesin in an anaesthetic dose has a depressant effect on the cerebral cortex which is mild but more prolonged than expected.

In conclusion, Althesin seems to have a powerful anticonvulsant action when tested on a model of generalized convulsion and on a model of focal convulsion. Our findings are in agreement with the report that this steroid agent has a depressant activity upon the reticular activating system and cerebral cortex and first description of the anticonvulsant properties of this agent on cardiazolic convulsions in cats (Bimar and Lepouleuf, 1973) and photic seizures in baboons (Emperaire and Bimar, 1973). Our data also support reports that Althesin was effective in treating status epilepticus (Munari et al., 1977; Alati et al., 1979) and suggest that a clinical history of convulsions must not be considered a contraindication to Althesin. Althesin also reduces intracranial pressure and brain oxygen consumption (Sari et al., 1976) and should be a useful anaesthetic for neurosurgery where partial or generalized seizures are common. The two examples of generalized convulsion following Althesin injection (Uppington, 1973; Rees, 1975) cannot be explained by the results of our study, but the suggestion that Althesin can cause a silent epileptic focus to discharge seems unlikely.

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REFERENCES


permis de prévenir et de traiter les crises dues à l'OHB. Les auteurs concluent que des antécédents cliniques de convulsions ne doivent pas être considérés comme une contre-indication à l'usage de cet anesthésique qui a des propriétés particulièrement utiles en neurochirurgie.

ANTIKONVULSIVE AKTIVITAT VON ALTHESIN AUF EXPERIMENTELLE EPILEPSIE

ZUSAMMENFASSUNG

ACTIVIDAD ANTICONVULSIVA DE LA ALTESINA EN EPILEPSIA EXPERIMENTAL

SUMARIO
Se llevaron a cabo ensayos sobre dosis anestésicas de Altesina en conejos usando dos modelos experimentales de epilepsia: generalizada (OHP; oxígeno en crisis inducida por presión alta) y parcial (crisis inducida corticalmente por penicilina). En ambos modelos, la Altesina siempre produjo una actividad anticonvulsiva que se reveló más potente en las convulsiones generalizadas. Este agente fue exitoso en el tratamiento y la prevención de las crisis OHP. Los autores concluyen que un historial clínico de convulsiones no debe considerarse como una contraindicación del uso de dicho anestésico que posee propiedades particularmente útiles en la neurocirugía.