ALTHESIN – A NEW INTRAVENOUS ANAESTHETIC

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IN 1941, Selye¹ noted the anaesthetic effect of some steroids in animals. Fourteen years later, Murphy *et al.*² reported on the use of a steroid – hydroxydione – to produce clinical anaesthesia. This agent, when given intravenously, has a gradual onset of action and produces prolonged sleep with little disturbance to the cardiovascular and respiratory systems and no hangover effect. Unfortunately, it causes an undesirably high incidence of venous irritation.

A new steroid anaesthetic, Althesin, has recently been introduced and promises to have many of the advantages of hydroxydione without its handicaps. Each ml of Althesin solution contains 9 mg of 3 α -hydroxy-5 α pregnane-11, 20-dione and 3 mg of 21-acetoxy-3 α -hydroxy-5 α pregnane 11, 20-dione; (see Figure 1). The latter (alphadolone) is half as potent as the former, but increases its solubility three times. The two steroids are dissolved in 20 per cent polyoxyethylated castor oil (Cremophor EL). The preparation is slightly oily to the touch and somewhat viscous but it can be comfortably injected through a 23-gauge needle and is non-irritant to the blood vessels.³ According to radio-active studies carried out by the manufacturers, Althesin is broken down rapidly in the liver. Inactive metabolites take five days to be excreted in the bile and urine. The drug crosses the placental barrier but there is a low concentration in the foetus, as compared with the mother. Althesin has been found to have a high therapeutic index.⁴

On injection of a clinical dose intravenously, there is a moderate fall in blood pressure with a rise in pulse rate. According to Campbell and associates⁵ there is no significant change in mean cardiac output. Prys-Roberts⁶ reported little change in peripheral vascular resistance but a depression of myocardial contractility of a degree similar to that produced by barbiturates and less than that caused by propanidid. In clinical dosage, there is slight hyperpnoea at induction, followed by hypopnoea (or apnoea with a large dose).

Althesin does not cause prolongation of the effects of suxamethonium, or interaction with other relaxants, and it is compatible with other anaesthetic agents.

METHOD

The present trial was carried out to study the clinical features and usefulness of this new anaesthetic. The drug was used to provide anaesthesia for a wide variety of operations and procedures not requiring the use of muscle relaxants. No patient received any volatile anaesthetic supplement and all patients breathed spontaneously throughout anaesthesia. Althesin was always administered on a

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FIGURE 1

dose per kg body weight basis; the dosage employed for induction ranged from 40 to 120 $\mu\text{l/Kg}$ and was injected in 25–30 seconds. The steroid was diluted with an equal part of normal saline, both in order to facilitate injection through a 23-gauge needle and also to make easier the accurate measurement of the dose. A record was made of the course of anaesthesia and at the completion of surgery the patient was taken to the recovery room where the stages of awakening and recovery were observed. Finally, a note was made of the incidence of post-operative complications, such as nausea and vomiting and venous complications.

Althesin has been used in a total of 258 patients. Their ages ranged from 6 to 80 years and the average age of the adults was 41.7 years; there were 19 patients under 16 years of age. The patients ranged in weight from 22 to 109 kg; the average weight was 61.3 kg. All patients were in good or moderately good physical condition and had no serious intercurrent disease.

Althesin was employed as the sole anaesthetic agent in 192 cases. A single dose of the drug sufficed for manipulation or a brief surgical procedure but for more prolonged operations, a further dose (or doses) was given as indicated, usually by movement in response to surgical stimulation, but sometimes because of inadequate hypnosis. The supplementary dose given was usually half the initial dose. Many of these 192 patients were day cases or out-patients: 31 had received atropine 0.6 mg with morphine 10 mg or meperidine 100 mg as pre-anaesthetic medication; the remainder had not been given any premedication. In a further 66 cases, expected to be of longer duration, Althesin was supplemented with nitrous oxide and oxygen. A measured dose per kg body weight of Althesin was injected and nitrous oxide: oxygen (6:2 litres(min.)) was administered by face mask throughout anaesthesia. Further doses of Althesin were administered later if required. Twenty-nine of the sixty-six cases who received nitrous oxide supplementation, had been given pre-anaesthetic medication as above.

RESULTS

When injected intravenously, Althesin produces sleep in one arm-brain circulation time; there is then a period of anaesthesia, usually with a variable duration of suppression of reflex response to surgical stimulation. During the first few minutes of anaesthesia, moderate to marked dilatation of the pupils is commonly present. With the onset of sleep there is usually good jaw relaxation and patency of the airway is impaired, so that the jaw must be supported. In four patients endotracheal intubation was performed after injection of 80–100 $\mu\text{l/kg}$ of Althesin

TABLE I
PROCEDURES PERFORMED UNDER ALTHESIN
ALONE (SINGLE DOSE)

Operation or Procedure	Number of Cases
Manipulation joint	39
Manipulation fracture $\pm$ P.O.P	29
Dental Extraction	25
Sigmoidoscopy	17
Incision abscess	14
Excision "lump"	14
D & C, etc.	8
Removal toenail	6
Injection of joint	5
Tendon operation	3
Removal screw, etc.	3
Division fraenum	2
ECT	1
Laparoscopy	1
Total	167

without muscle relaxant, but this was not considered to be an advantageous method of intubation. Table I shows the number and nature of the operations performed under anaesthesia with Althesin alone. The duration of the surgical procedures ranged from 15 seconds to 29 minutes and averaged 3.9 minutes. Of the 167 patients who received a single dose of the anaesthetic, anaesthesia was satisfactory in 119; in a further 33, there was some movement in response to stimulation and in the remaining 15 patients surgical stimulation produced considerable reflex response with or without phonation, and restraint was necessary to complete surgery without supplementation.

Recovery from anaesthesia was usually smooth and uneventful. Jaw tone and reflexes return early and the eyes open, and then for several minutes the patient replies to his name but is unaware of where he is and why.

Complications and Side-Effects

In no patient was local irritation of tissues or venous irritation noted. Nausea occurred in seven patients and nausea plus vomiting in six patients who received Althesin with premedication and/or nitrous oxide supplementation. In five patients there were emetic symptoms after Althesin alone. Coughing occurred at induction in 11 patients, seven of whom had not received premedication. Muscle-twitching and convulsive muscle movements were noted in 69 patients shortly after induction. This muscular activity did not usually interfere with the positioning of the patient or with surgery. In a few patients surgical stimulation evoked a convulsive response. Muscular excitability seemed to be less common in the patients who had been given premedication, and was clearly dose-related. Hiccup occurred during induction in 19 patients and in five patients hiccup occurred early in the recovery phase; it was usually transient and did not interfere with anaesthesia or operation. It occurred more often with the larger doses.

Other Side-Effects

In seven patients an erythematous rash developed on the neck and upper chest

TABLE II
DOSE-DURATION RESPONSE

Dose of Althesin	No. of patients	Time of injection to:		
		Eyes open	Orientation	Sitting up
		Min.	Min.	Min.
40 μ l/Kg	11*	4.4	6.5	6.6
60 μ l/Kg	27	6.4	9.2	10.5
80 μ l/Kg	30	8.4	12.7	14.2
100 μ l/Kg	27	10.0	15.4	15.7

* All aged over 40 years.

shortly after induction of anaesthesia; it disappeared without special treatment. Ten patients exhibited marked shivering during the recovery stage. In six patients there was marked salivation; one of them received the drug on a subsequent occasion and again developed marked salivation. The incidence of side-effects appears to be dose-related.

Recovery

A study was made of recovery from anaesthesia in patients aged 15-59 years inclusive, who had received a single dose of 40, 60, 80 or 100 μ l/Kg of Althesin. The method of assessment has already been reported elsewhere.⁷ Briefly, following completion of the operation the patient was asked at 15-second intervals to open his eyes and when he responded to this command, he was then asked at frequent intervals to say where he was ("orientation") and to sit up (unaided). The recovery data thus obtained were submitted to statistical analysis. Table II shows the mean times from commencement of the injection of the anaesthetic ("0") to the time of the various phases of recovery. Each of the three measures of recovery showed a significant increase when the dose changed from 40 to 60 μ l/Kg and from 60 to 80 μ l/Kg. This pattern appears to continue to a lesser extent when the dose is increased to 100 μ l/Kg, but there is also an underlying pattern of greater variability as the dose level increases and in consequence none of the differences between the effects of 80 and 100 μ l/Kg is significant. The investigation revealed no evidence of a difference in response to Althesin between males and females.

Finally, the recovery data were also analysed in relation to age, results in those under 40 being compared with those over 40 years old. There was a clear pattern of longer duration in those over 40 compared with those under 40 years, particularly in regard to time from "0" to "eyes open" and time from "0" to "orientation", but the results did not reach the 0.05 level of significance.

DISCUSSION

On the clinical side, the results of this work suggest that Althesin is a satisfactory and safe intravenous anaesthetic agent, both for induction of anaesthesia and use in minor surgery. In the majority of patients a single dose of 50 to 80 μ l/Kg will provide a few minutes of useful surgical anaesthesia and there is reasonably rapid recovery. In a number of patients muscular movements and reflex

response to surgery result in less than satisfactory anaesthesia, and in some cases relaxation is inadequate for such procedures as manipulation of joints. In the dose response study we found that there is a direct relationship between dosage and duration of effect and that the larger the dose the greater is the variability in duration of effect. It was also found that the duration of effect with any dosage appears to be longer in those aged over 40 than in younger patients; the same relationship to age was found in a previous study with propanidid.⁸ No difference was found between the duration response to Althesin of males and females; this is particularly interesting because with propanidid we found a significant difference between the response of males and females, and Dundee⁹ also found that male patients required a larger dosage per body weight of thiopentone than did females of comparable age and weight.

This new steroid agent differs markedly from the previous steroid anaesthetic, hydroxydione² which had a delayed onset and prolonged duration of action and which caused a high incidence of venous irritation. Althesin seems to be broken down fairly rapidly, but recovery from anaesthesia differs somewhat from that following barbiturate or propanidid anaesthesia.⁹ The recovery of consciousness and orientation is much slower than with these latter two, which suggests that redistribution does not in itself lower the blood and brain level sufficiently for recovery of consciousness. On the other hand, the time to full recovery and ambulation is of the same order as with other types of intravenous anaesthetic agents.¹⁰ Unlike previous intravenous anaesthetics investigated, it was often found that after Althesin the patient could sit and even stand unaided while still not "orientated". In out-patients, recovery must be carefully assessed before allowing patients to go home.

As with the previous intravenous anaesthetics, the incidence of excitatory phenomena increased with dosage and is higher in patients who have not received pre-medication.¹¹ The incidence of nausea and vomiting after Althesin is low and the absence of local irritation is advantageous. However, the occurrence of marked salivation in some patients suggests that pre-anaesthetic administration of atropine is advisable. In view of the fact that the higher doses of the anaesthetic produced an increased incidence of side-effects without a corresponding increase in operating time, a dosage range of 50–80 μ l/Kg would normally appear to be adequate. Cremophor EL is obviously not an ideal solvent, having side-effects of its own, and it is to be hoped that a better solvent will be found.

In conclusion, this new steroid anaesthetic is an interesting one and the results obtained in this study suggests that the drug is sufficiently promising to justify more extensive clinical trials to determine its value, especially in relation to the intravenous induction of general anaesthesia.

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