Clinical Studies with Althesin (CT 1341) in Minor Operative Procedures*

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SUMMARY

A brief history of the introduction of, and advances in, intravenous steroid anaesthesia is related. Althesin, the most recent drug, was used as the sole anaesthetic in 61 minor gynaecological procedures in 2 dose levels (0,1 ml and 0,15 ml/kg). The lower dose was found to give adequate anaesthesia for only 5 minutes, while the larger dose lasted for 7 minutes, but produced a significant fall in arterial oxygen tension. With both dosages Althesin caused significant rises in pulse and respiratory rates and a slight fall in blood pressure. Recovery was rapid and usually pleasant.

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In 1941 Hans Selye[1] conducted a series of experiments in order to learn more about the pharmacological effects of acute overdosage with steroids. He noted that the various steroid hormones, especially desoxy-corticosterone acetate (DCA) and progesterone, produced deep anaesthesia when injected into the peritoneum of rats and mice, and that after recovery these animals showed no ill-effects. These findings, however, remained of academic interest until 1955 when Laubach, P'an and Rudel[2] studied a number of new water-soluble steroids in order to determine their anaesthetic activity. Of these steroids, 21-hydroxy-pregnanedione-sodium succinate (hydroxydione) was the most promising.

The first clinical trials of hydroxydione were conducted in the USA by Murphy *et al.*,[3] Gordon *et al.*,[4] in 1955, and Howland *et al.* in 1956.[5] The advantages claimed for this type of anaesthetic were a high therapeutic index, lack of respiratory depression within clinical dosage, quiescence of laryngeal, pharyngeal and bronchial reflexes, the ease with which intermittent positive pressure ventilation could be effected, and the relatively pleasant recovery for the patient.[6] The disadvantages were the slow rate at which hydroxydione dissolved, a marked tendency to thrombophlebitis, the slowness of induction and recovery, the rise in pulse rate and occasional falls in blood pressure.

Because of these disadvantages, steroid anaesthesia was once again reduced to the level of academic interest, until the discovery of Althesin (CT 1341) in 1971.[7] Althesin is, in fact, a combination of two pregnanediones, both with anaesthetic activity. This mixture is used because the 21-acetoxy compound greatly increases the solubility of the 3α hydroxy compound in the vehicle, cremophor EL. The formulation is:

1. 3α hydroxy-5α-pregnane-11,20 dione ... 0,9% w/v
2. 21-acetoxy-3α-hydroxy-5α- pregnane-11,20 dione ... ... 0,3% w/v
3. Cremophor EL (polyoxethylate castor oil) ... ... 20% v/v
4. Sodium chloride ... ... 0,25% w/v
5. Water for injection ... ... to 100%

Althesin contains 12 mg of total steroid per millilitre.

Investigation of Althesin in a wide variety of laboratory animals[7] has shown the mixture to be rapidly active, of short duration and with few side-effects. In particular, it was found to be non-irritating to arteries and veins. A subsequent study on volunteers[8] and further clinical trials,[9,10] have shown that it causes no severe systemic or local toxic effects in the clinical dose range, and that recovery is rapid and uncomplicated.

The aim of this trial was to evaluate the role of Althesin when used as the sole anaesthetic agent for short operative procedures in patients breathing air.

METHOD

The patients, whose ages ranged from 21 to 42 years, underwent minor gynaecological procedures and were well, apart from their primary pathology. Consent was obtained for the use of the new agent and no premedication was given. In the ward, and also before induction, systolic blood pressure, pulse and respiratory rates were measured. An electrocardiograph was used to record pulse rate and arrhythmias during the anaesthesia. Following induction, measurements of vital parameters were made at 1-minute intervals. Patients were divided into 3 groups:

Group 1 comprised 28 patients given 0,1 ml/kg bodyweight.

Group 2 comprised 21 patients given 0,15 ml/kg bodyweight.

Group 3 comprised another 12 patients, given 0,15 ml/kg bodyweight, in whom intra-arterial cannulae were placed for measurement of blood gases by the Astrup method, and for measurement of mean intra-arterial pressures by means of an aneroid manometer previously standardized against a mercury manometer. These were the only measurements made in this group.

The duration of surgery was noted as being the time in which the patient was in the lithotomy position.

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Recovery time was that time at which patients were able to respond to commands, to either stick out their tongues, or open their eyes. The time at which they became spatially orientated was also noted. The patients were questioned immediately afterwards, as well as later in the wards, as to their mood, memory of the anaesthetic, dreams, and incidence of nausea and vomiting.

RESULTS

Surgery commenced 2¾ minutes after induction in group 1 and after 2¼ minutes in group 2. Changes in some parameters must be related to this stimulus. Anaesthesia was judged to be satisfactory from a surgical point of view, if no or minimal movement took place in response to surgical stimulus.

Thus, with the smaller dose in group 1, satisfactory anaesthesia was produced for only 5 minutes, and if surgery was prolonged beyond this time, supplementation of one-third of the induction dose was given. Only 11% did not move at all and a further 25% made only slight movements—the procedure in the above 36% lasting only 6 minutes. In the remaining 64% enough movement took place to make surgery difficult, and so additional increments of Althesin were given; this supplementation taking place an average of 5 minutes after induction. The procedure in these 64% took 10 minutes.

In group 2 anaesthesia was satisfactory in 80%—33% did not move at all and 47% moved only slightly. The procedures lasted an average of 7 minutes.

Airway

Chin support was required in approximately half the cases—61% in group 1 and 43% in group 2.

Laryngospasm did not occur, but 1 patient in each group had a bout of coughing after induction. Salivation was not a problem.

Hiccough occurred in 29% of group 1 and 43% of group 2.

Intubation was attempted in 3 patients in each group, and was unsuccessful in all cases. The masseters were relaxed and the larynx easily visualized, but introduction of an endotracheal tube was resisted by adduction of the cords.

Pre-induction means in blood pressure, pulse and respiratory rates were used as baselines to assess all changes occurring thereafter—significant increases had already taken place in these measurements after leaving the ward. The statistical significance of changes was assessed by means of the Student *t*-test.

Respiratory Rate (Table I)

A tachypnoea occurred in both groups and this did not return to normal before the patients left for the ward. After induction, ventilation became very shallow, and in 14% of group 1, and 19% of group 2, patients became apnoeic for a few seconds. In only 1 case, in group 1, was it felt necessary to ventilate with oxygen for 2 minutes.

TABLE I. THE EFFECT OF ALTHESIN ON RESPIRATORY RATE

	Mean pre-induction rate	Mean maximum rate	Mean % increase
Group 1			
Rate/min	**24**	**42 at mean time of 4 min**	**75**
SD	**± 6,5**	**± 11,5**	**$P<0,001$**
Group 2			
Rate/min	**21**	**40 at mean time of 4 min**	**90**
SD	**± 3,6**	**± 8**	**$P<0,001$**

Blood Gases (Table II)

In group 3 in which blood gases were studied with patients breathing air after a dose of Althesin 0,15 ml/kg, a hypoxaemia occurred in the first 3 minutes. Thereafter the PaO_2 increased, though it did not return to pre-induction levels during recovery.

There were no significant changes in $PaCO_2$ levels during anaesthesia.

TABLE II. THE EFFECT OF ALTHESIN ON BLOOD GASES IN GROUP 3 PATIENTS

	Pre-induction	3 min	6 min	9 min	12 min
PaO_2 (mmHg)	**100**	**75**	**85**	**87**	**89**
		25% fall $P<0,01$			
$PaCo_2$ (mmHg)	**32**	**35**	**35**	**36**	**34**

Heart Rate (Table III)

There was a tachycardia in both groups after induction—a 23% increase by 2 minutes in group 1 and a 28% increase by 3 minutes in group 2. In both groups the rate had declined to pre-induction levels by recovery.

Electrocardiogram

Only 1 tracing, in group 2, showed an abnormal ECG after induction. This patient developed ventricular premature systoles, which at times coincided with hiccoughs. No treatment was required. One patient with ventricular premature systoles before induction continued the arrhythmia after being given Althesin.

Blood Pressure

Within 2 minutes Althesin produced a 15% (group 1) and 21% (group 2) fall in systolic blood pressure. With dilatation of the cervix the blood pressure started to rise, and it reached pre-induction levels by 5 - 6 minutes, and stayed at that level through recovery.

This initial hypotension was confirmed by intra-arterial pressure measurements, the fall being from 98 mmHg to 75 mmHg within 2 minutes.

TABLE III. THE EFFECT OF ALTHESIN ON HEART RATE

	Mean pre-induction rate	Mean maximum rate	Mean % increase	Mean final rate
Group 1				
Rate/min	**101**	**124 at 2 min**	**23**	**109 at 12 min**
SD	**± 16**	**± 16**	**$P<0{,}001$**	**± 17**
Group 2				
Rate/min	**93**	**119 at 3 min**	**28**	**103 at 12 min**
SD	**± 20**	**± 17**	**$P<0{,}001$**	**± 24**

TABLE IV. THE EFFECT OF ALTHESIN ON BLOOD PRESSURE

	Mean pre-induction pressure	Mean minimum pressure	Mean % decrease	Mean final pressure
Group 1				
Mean systolic BP (mmHg)	**134**	**115 at 1½ min**	**15**	**128 at 12 min**
SD	**± 17**	**± 11**	**$P<0{,}001$**	**± 14**
Group 2				
Mean systolic BP (mmHg)	**134**	**106 at 2 min**	**21**	**125 at 14 min**
SD	**± 24**	**± 18**	**$P<0{,}001$**	**± 20**
Group 3				
Mean arterial pressure	**98**	**75 at 2 min**	**23**	**94 at 9 min**
SD	**± 30**	**± 27**	**$P<0{,}001$**	**± 27**

Recovery

In group 1, the 12 non-supplemented cases responded to commands by 10 minutes and were orientated by 15 minutes. Supplementation in the other 16 cases delayed recovery—they responded by 15 minutes and were orientated by 17 minutes.

The group 2 cases responded by 13 minutes and were orientated by 25 minutes.

Euphoria was noted in only a small percentage of cases—14% in group 1 and 19% in group 2. Most patients (68% in group 1 and 71% in group 2) lay quietly and appeared drowsy.

Pain was experienced by 20% of patients in each group during recovery and shivering occurred in a small percentage (14% in group 1 and 10% in group 2).

Nausea was experienced by 7 patients in group 1 and 2 patients in group 2. One of these group 2 patients vomited during recovery.

When seen later in the ward, all patients had completely recovered and none had found the anaesthetic unpleasant. nor experienced hallucinations or dreams.

DISCUSSION

In this trial an attempt was made to use Althesin as the sole anaesthetic in minor cases. In group 2, a larger dose than that usually used in earlier trials was tried, as well as being compared with the commonly recommended dose of 0,1 ml/kg. Only in the higher dose was the response during surgery satisfactory in most cases. Unlike Clarke *et al.*[9] we found anaesthesia more satisfactory with the higher dose. Muscle movements appeared to be associated with insufficient depth of anaesthesia, rather than with an increased dose of Althesin.

As in most trials, we found a significant drop in blood pressure, with a return to normal levels on surgical stimulation, as well as an increase in heart rate. However, according to Campbell and his associates[8] there is no significant change in cardiac output. Arrhythmias have not been reported in other trials, but 1 of our patients developed ventricular premature systoles during anaesthesia.

The 90% increase in respiratory rate in group 2 differs quite considerably from that of the patients in the trial by Savage *et al.*,[11] where the increase was only 53% using the same dose.

Clarke *et al.*[9] did not notice any respiratory depression in their patients, using a dose of 0,2 ml/kg. In contrast to this, 19% of our group 2 patients became apnoeic, though this was of short duration and did not require artificial ventilation. Half of our patients lost the ability to maintain a patent airway and required chin support. The airway remained satisfactory, with no laryngospasm or bronchospasm. Unlike Swerdlow *et al.*[12] we found no increase in salivation. Hiccoughing was a significant problem and appeared to be dose-related, as shown by Clarke *et al.*[9]

Hypoxaemia was shown with the larger dose, but it must be remembered that these patients were breathing air without additional oxygen, and at a PaO_2 of 75 mmHg haemoglobin is usually 90% saturated.

Recovery was rapid and uncomplicated and within

half an hour all our patients were well enough to be left on their own.

If no ischaemic changes following accidental intra-arterial injection are reported, and it can be shown that the drug is not porphyrinogenic, it will become a useful drug in the anaesthetist's armamentarium.

In conclusion we have found Althesin to be an acceptable induction agent; but to be satisfactory as the sole anaesthetic in short procedures only when the larger dose is used.

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