Althesin (CT 1341) – A New Intravenous Anaesthetic Agent*

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SUMMARY

Althesin (CT 1341), a new intravenous steroid anaesthetic agent without steroid activity, was given as induction agent to a total of 104 patients and the side-effects noted. Two dosage ranges were used and the side-effects compared. The drug was found to be a safe induction agent, but side-effects were often troublesome. It can be used as a substitute for thiopentone sodium, especially in patients who are going home the same day.

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The first intravenous anaesthesia was given in 1874 by Oré, who used chloral hydrate. Since then several agents have been tried, e.g. paraldehyde, ethyl alcohol, and magnesium sulphate, with varying success, but the breakthrough came with the introduction of the barbiturates, especially the ultra short-acting thiopentone sodium, which was first used by Lundy of the Mayo Clinic in 1934. Although widely used throughout the world with great success, thiopentone sodium can be a dangerous agent in the hands of the inexperienced, and the search for a safe intravenous induction agent still continues.

In 1941 Selye found that certain of the steroids he was studying possessed anaesthetic properties, but it was only in 1955 that 21-hydroxypregnanedione sodium succinate (Viadril), was used in man. Although it offered a smooth anaesthesia and had a high therapeutic index, it had certain disadvantages. Unconsciousness occurred only 2 - 10 minutes after intravenous administration, and many patients developed thrombophlebitis,[1] with the result that its use was abandoned.

With the introduction of Althesin, a steroid anaesthetic agent, new interest has awakened in steroid anaesthesia. Child *et al.*[2] investigated the agent in animals, and found that it might safely be used as an induction agent. Campbell *et al.*[3] reported favourably in man, and recommended further trials on patients.

PHARMACOLOGY

Althesin is composed of two steroid agents:

Steroid I: 3α hydroxy-5α pregnane-11, 20-dione—0,9% w/v; and

Steroid II: 21 acetoxy-3α-hydroxy-5α pregnane-11, 20 dione—0,3% w/v.

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The steroids are dissolved in Cremophor EL—20% v/v, sodium chloride AR—0,25% w/v, and water for injection BP 10 100%.

The structural formulae of the two steroids are shown in Fig. 1.

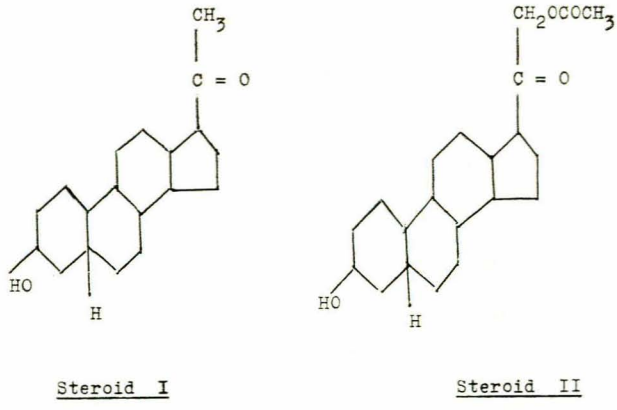

Fig. 1. See text.

Both steroids contain anaesthetic properties, but steroid II possesses 47% of the activity of steroid I, which renders it more soluble in Cremophor EL, which is polyethylated castor oil.

Each millilitre of Althesin contains 9 mg of steroid I and 3 mg of steroid II, and we found it easier to express the dosage in ml/kg bodyweight.

METHOD

The trial was carried out at H. F. Verwoerd Hospital. A total of 104 patients received the anaesthetic agent. Most of the patients were undergoing minor surgical procedures and investigations, as shown in Table I. Table II summarizes the sex, average age and weight of all the patients. Of the 104 patients, 53 received no premedication whatsoever, 18 received 0,6 mg atropine 1 hour preoperatively, and 33 received atropine 0,6 mg plus some kind of light sedation, which consisted of either pethidine, promethazine, diazepam or hydroxyzine, as summarized in Table III.

The trial was conducted in three separate phases. During the first phase Althesin was used as an induction agent

TABLE I. OPERATIONS OR PROCEDURES PERFORMED UNDER ANAESTHESIA WITH ALTHESIN

Operations or procedures	Anaesthetic: 0,06 ml/kg + halothane	0,1 ml/kg + halothane	0,1 ml/kg breathing air
Scope and retrograde pyelogram	31	26	0
D + C	0	4	22
Bilat. Cockett	0	1	0
Bronchoscopy	0	1	0
Oesophagoscopy	0	1	0
Abd. lipectomy	0	1	0
Commando operation	0	1	0
Mastectomy	0	1	0
Biopsy vulva	0	1	0
Removal tumour leg	0	1	0
Abd. hysterectomy	0	1	0
Ant. + post. vag. repair	0	1	0
Circumcision	0	1	0
Transurethral resection	5	0	0
Thyroidectomy	2	0	0
Biopsy tumour mamma	2	0	0
Urethra dilatation	1	0	0
	41	41	22

and the dosage used was 0,1 ml/kg bodyweight. Before induction, the pulse rate, blood pressure readings and respiratory rate were observed and the patient connected to a cardioscope. The rate of injection of Althesin was always the same and the injection completed in 30 seconds. Unconsciousness occurred within one arm-brain circulation time. After induction the patients were closely observed for changes in heart rate, respiratory rate, blood pressure, pharyngeal and laryngeal reflexes, pupillary size and side-effects, especially apnoea, respiratory depression, cardiac arrhythmias, ECG changes, hypotension, involuntary movements, tremors, twitching, hiccough, vomiting and salivation. While these observations were recorded, nobody was allowed to stimulate the patients. Any changes in blood pressure, pulse rate, respiratory rate, etc. immediately after induction were thus not caused by surgical stimulation. The anaesthesia was then supplemented with halothane (1 - 2%) N_2O and O_2, and only then was the surgeon allowed to proceed.

TABLE III. PRE-MEDICATIONS GIVEN

Phase	No premedication	Atropine only	Atropine + sedation
1	20	4	17
2	17	8	16
3	22	0	0

After 41 patients had been anaesthetized in this way, it was decided to reduce the dosage from 0,1 ml/kg bodyweight to 0,06 ml/kg, to see whether the incidence of side-effects could be reduced. This was the second phase of the trial.

In the third phase of the trial, Althesin was used as the sole anaesthetic agent, with the patient breathing air during the whole surgical procedure.

After the surgical procedure, all the patients were taken to the recovery room, where they were observed by competent nursing staff who immediately reported any unfavourable side-effects. The time when the patients were able to respond to instructions was noted. Most of the patients were in good condition pre-operatively, although some suffered from compensated chronic cardiac failure, hypertension, chronic bronchitis and diabetes.

Each induction was classified under one of four grades as used by Clarke *et al.*:[4]

Grade 1: Smooth induction without any side-effects.

Grade 2(a): Side-effects which did not interfere with the anaesthesia or surgical procedure.

Grade 2(b): Side-effects which interfered with the anaesthesia or surgical procedure, but did not endanger the patient's life.

Grade 3: Side-effects which could endanger the patient's life.

Grade 1 and 2(a) were considered acceptable inductions, and grade 2(b) and 3 unacceptable.

TABLE II. SEX, AVERAGE AGE AND WEIGHT OF PATIENTS RECEIVING ALTHESIN

Phase	Anaesthetic	Sex: M	Sex: F	Age in years	Weight in kg
1	0,1 ml/kg + halothane N_2O, O_2	21	20	52	71
2	0,06 ml/kg + halothane N_2O, O_2	20	21	52	73,5
3	0,1 ml/kg breathing air	0	22	26	59
	Group as a whole	41	63	46,5	69,5

RESULTS

Phase I

During phase I, 41 patients received 0,1 ml/kg Althesin as induction agent. Twenty-four patients did not receive any sedation pre-operatively, and 17 received some kind of light sedation. Anaesthesia was maintained with halothane, N_2O and O_2. The percentage incidence of side-effects is summarized in Tables V and VI.

Eighteen patients (44%) developed apnoea, which in 2 cases lasted 2 minutes while respiration was being assisted. The other cases were of short duration, which did not warrant intervention and did not interfere with the anaesthesia. Of the 41 patients, 26 (63%) developed respiratory depression of a minor nature and in only 2 patients was it necessary to assist respiration. Of the 24 patients who did not receive any pre-operative sedation, 14 (58%) developed apnoea. Of the 17 patients who received pre-operative sedation, 12 (70%) developed apnoea; the respiratory rate increased by 63% but a fall in tidal volume accounted for the respiratory depression.

There was an average fall of 12% in systolic blood pressure and a 20% rise in pulse rate. After introduction of halothane the pulse rate usually dropped, and in patients who did not receive atropine pre-operatively, some fell well below the pre-operative rate, and atropine had to be given.

Involuntary movements, twitchings or tremors, occurred in 15 patients (36,6%), which were so severe in 4 patients that this interfered with both the anaesthesia and surgery. These movements occurred immediately after injection of Althesin and before surgical stimulation, and we do not agree with Bradford *et al.*[5] and Campbell *et al.*[3] who suggested that these excitatory phenomena might possibly be due to surgical stimulation. Hiccough occurred in 5 patients (12%), 4 of whom did not have any pre-operative sedation. It therefore seems likely that pre-operative sedation might reduce this side-effect.

Cardiac arrhythmias were observed in 6 patients (15%); 5 patients developed atrial extrasystoles soon after injection of Althesin, but these disappeared before the end of the surgical procedure; 1 patient developed ventricular extrasystoles. This patient had a carcinoma of the

TABLE IV. PERCENTAGE INCIDENCE OF DIFFERENT GRADES OF INDUCTION ACCORDING TO DOSAGE

	Acceptable			Unacceptable		
Dose (ml/kg)	Grade 1 (%)	Grade 2(a) (%)	Total (%)	Grade 2(b) (%)	Grade 3 (%)	Total (%)
0,06	58,5	36,5	95	2,5	2,5	5
0,1	41	46	87	11	2	13

TABLE V. PERCENTAGE INCIDENCE OF SIDE-EFFECTS WITH ALTHESIN

	Anaesthetic		
Side-effects	Phase 1 (0,1 ml/kg)	Phase 2 (0,06 ml/kg)	Phase 3 (0,1 ml/kg breathing air)
Respiratory depression	63	36,5	0
Apnoea	44	29	0
Involuntary movements	36,6	17	23
Hiccough	12	2,5	5
Cardiac arrhythmias	15	7	0
Salivation	5	0	9
Coughing	5	5	5

TABLE VI. EFFECT OF ALTHESIN ON BLOOD PRESSURE, PULSE RATE AND RESPIRATORY RATE, EXPRESSED AS PERCENTAGE FALL OR RISE

	Anaesthetic		
	Phase 1 (0,1 ml/kg)	Phase 2 (0,06 ml/kg)	Phase 3 (0,1 ml/kg breathing air)
Blood pressure	−12	−12	−10
Pulse rate	+20	+18	+22
Respiratory rate	+63	+50	+42

bronchus, developed severe involuntary movements as well as apnoea, and in spite of adequate controlled ventilation, began having 10 ventricular extrasystoles per minute, which lasted for 2 minutes. This patient also received suxamethonium chloride and the arrhythmia cannot definitely be ascribed to the Althesin.

Salivation was observed in 2 patients, both obese, and because the airway could not be maintained, they had to be intubated after the administration of suxamethonium chloride. Neither patient received any atropine pre-operatively.

No patients complained of nausea and there was no vomiting. Most of the patients developed widely dilated pupils which constricted again after halothane administration.

If we classify the induction during phase I according to Clarke's gradation, we find the following:

10 patients (24,5%) fell under grade 1;
25 patients (61%) fell under grade 2(a);
5 patients (12%) fell under grade 2(b); and
1 patient (2,5%) fell under grade 3.

Therefore 85,5% were acceptable inductions, and 14,5% unacceptable.

Phase II

In an attempt to reduce side-effects, it was decided to give the following 41 patients a reduced dosage of 0,06 ml/kg. In all other aspects the trial was conducted in exactly the same way as in phase I. Of the 41 patients, 25 did not receive any sedation, and 16 received light sedation pre-operatively.

Twelve patients (29%) developed apnoea, which in 1 case lasted 5 minutes. In the remaining cases, apnoea was of such short duration that intervention was not necessary. Respiratory depression developed in 15 patients (36,5%), lasted a short period, and assisted respiration was not necessary. Of the 25 patients who received no pre-operative sedation, 7 (28%) developed apnoea. Of the 16 patients who received sedation 8 (50%), developed apnoea. Again it seems that sedation is a contributing factor in the development of apnoea. The respiratory rate increased by an average of 50%.

There was an average fall in systolic blood pressure of 12%, the same as in phase I. One patient went into a state of shock after the induction, and no blood pressure could be recorded. She was suffering from hyperthyroidism, compensated cardiac failure and mild hypertension, and was under treatment with digoxin, furosemide, Neo-Mercazole and propranolol. There were several other compensated cardiac failure patients in the series who gave no trouble at all. This was the only patient who received a beta-blocking agent. This might suggest that the cardiovascular system is dependent on sympathetic activity after induction with Althesin.

There was an average increase in pulse rate of 18%. Two patients developed atrial extrasystoles immediately after induction; these disappeared after 2 minutes. One patient developed 12 ventricular extrasystoles per minute after inhaling 2,5% halothane in an attempt to deepen anaesthesia. The concentration of halothane was reduced, 50 mg lignocaine was given intravenously and the arrhythmia disappeared.

Involuntary movements, twitching or tremors occurred in 7 patients (17%), but all were of a minor nature. Salivation was not observed in any patient. Hiccough was observed in one patient (2,5%). There was no vomiting and no complaint of nausea was made. The pharyngeal and laryngeal reflexes were intact most of the time.

If we classify the inductions, we find the following:

24 patients (58,5%) fell under grade 1;
15 patients (36,5%) fell under grade 2(a);
1 patient (2,5%) fell under grade 2(b); and
1 patient (2,5%) fell under grade 3.

Therefore, 95% were acceptable inductions and 5% unacceptable (see Table IV).

Phase III

The third phase was conducted to find out: (*a*) whether Althesin could be used as the sole anaesthetic agent for short surgical procedures; (*b*) what the dosage would be for such a procedure; and (*c*) what the duration of action of Althesin is.

Twenty-two Bantu patients undergoing dilatation and curettage for incomplete abortion, were given Althesin as the sole anaesthetic agent, while breathing air. All the patients were young and in good health, the average age being 26 years. The dosage decided on was 0,06 ml/kg, but after 3 patients, it was decided to increase the dosage to 0,1 ml/kg, because the patients reacted to surgical stimulation. No patient received any form of sedation or atropine pre-operatively. The operative procedure started 3 minutes after induction and lasted an average of 5 minutes. It was not necessary to give a second dose to any of the patients who received 0,1 ml/kg.

There was an average fall in blood pressure of 10%. The pulse rate increased by 22% and remained elevated to the end of the operation. No cardiac arrythmias were encountered. The respiratory rate increased by 42%. The amazing finding was that no patient developed apnoea or respiratory depression. One patient had induction excitation. Involuntary movements were noted in 5 patients (23%), but this did not interfere with the surgical procedure. Hiccough occurred in 1 patient and salivation in 2 patients. There was no nausea or vomiting.

If we classify the inductions, we find the following:

16 patients (73%) fell under grade 1;
4 patients (18%) fell under grade 2(a);
2 patients (9%) fell under grade 2(b); and
No patients fell under grade 3.

Therefore, 91% were acceptable inductions and 9% unacceptable.

The percentage incidence of different grades of induction according to dosage is summarized in Table IV. For this purpose the patients in phases I and III of the trial were combined, because the induction dose had been the same in both phases.

DISCUSSION

Animal investigations done by Child *et al.*[2] suggested that Althesin could safely be used as an anaesthetic agent in man. Trials conducted by various investigators were favourable, and Campbell *et al.*[3] Bradford *et al.*[5] and Swerdlov *et al.*[6] suggested that the drug was worthy of further trial.

During the limited trial done by us, we were impressed with the use of this drug in minor surgical procedures. There was an average fall in systolic blood pressure of 12%, compared with 10% found by Swerdlov *et al.*[6] and no blood pressure fell lower than 33%, except in the patient who received propranolol. The few patients who suffered from compensated cardiac failure presented no problems. The fall in blood pressure was not influenced by alteration of dosage. There was an average increase in pulse rate of 20%. The maximum increase occurred immediately after induction. The rate decreased soon after induction, but usually remained above the initial pre-operative rate. Where atropine was omitted in the premedication and halothane used after induction, the rate sometimes fell well below the initial value and atropine had to be given. It is suggested that atropine be given pre-operatively where halothane is also to be used, but if Althesin is the sole anaesthetic agent, atropine can safely be omitted. Salivation was not a problem; it only occurred in the higher dosage range of Althesin, and was not marked.

As can be seen from Table V, there was a high incidence of apnoea and respiratory depression, which was clearly dose-related. There was also a higher incidence of respiratory depression in patients who received pre-operative sedation. Apnoea and respiratory depression were usually moderate and of short duration. The fact that none of the Bantu women developed apnoea or respiratory depression cannot be explained. Four factors seem to have played a role: the average age of the Bantu patients was 26 years, and those of phases I and II, 52 years; no sedation was given to any patient pre-operatively; all the patients were in good physical condition, whereas many patients in phases I and II were suffering from some form of pathology; and all the patients were Bantu women, whereas all the patients in phases I and II were Whites.

The respiratory rate increased by ± 50% and was not influenced by alteration of dosage.

Rather a high percentage of the patients developed involuntary movements. As can be seen from Table V, the movements were clearly dose-related. In phase I of the trial the movements were so severe in 4 patients that they interfered with surgery. Light sedation did not prevent involuntary movements. Of all the side-effects encountered during the trial, we found the involuntary movements, twitchings and tremors the most disturbing.

Of the patients in phase I, 12% developed hiccough; of those in phase II, 2,5%, and those in phase III, 5%. Light sedation did not seem to reduce this side-effect. Directly after induction, 5% of the patients started coughing. The laryngeal reflexes were present in most of the patients who received the lower dosage of 0,06 ml/kg, but absent when 0,1 ml/kg was used. There was marked dilatation of the pupils directly after induction, but they became small after introduction of halothane.

The length of action of Althesin could be observed in phase III, where the drug was used as the sole anaesthetic agent and only one injection was given. The length of action was found to be approximately 12 minutes. In phases I and II where halothane was also used, the patients were awake 10 - 12 minutes after completion of the operation. Recovery was uneventful and the patients did not suffer any 'hangover'. This is an advantage over thiopentone sodium. No nausea or vomiting was observed throughout the trial, and thrombophlebitis did not occur in any patient.

We consider Althesin a safe anaesthetic agent, although some side-effects were troublesome. It can be used as a substitute for thiopentone sodium as an induction agent, and also as the sole anaesthetic agent for very short surgical procedures, especially where the patient is expected to go home the same day.

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REFERENCES

1. Murphy, F. J. and Guadagna, N. P. (1955): J. Amer. Med. Assoc., **158**, 1412.
2. Child, K. J., Currie, J. P., Davis, B., Dodds, M. G., Pearce, D. R. and Twissel, D. L. (1971): Brit. J. Anaesth., **43**, 2.
3. Campbell, D., Forrester, A. C., Miller, D. C., Hutton, I., Kennedy, J. A., Lawrie, T. D. V., Lorimer, A. R. and McCall, D. (1971): *Ibid.*, **43**, 14.
4. Clarke, R. S. J., Montgomery, S. J., Dundee, J. W. and Bouill, J. G. (1971): *Ibid.*, **43**, 947.
5. Bradford, E. M. W., Miller, D. C., Campbell, D. and Baird, W. L. M. (1971): *Ibid.*, **43**, 940.
6. Swerdlov, M., Chakraborty, S. K. and Zahangir, M. A. H. M. (1971): *Ibid.*, **43**, 1075.