Althesin (CT 1341) : intravenous anaesthetic.

VD

ALTHESIN

(CT1341)

Intravenous anaesthetic

Glaxo

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(CT 1341)

Intravenous anaesthetic

Glaxo

GLAXO LABORATORIES LIMITED

Greenford, Middlesex

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Acknowledgements

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The British Journal of Anaesthesia:
Figure 3, page 8; Figure 4, page 12
Table 3, page 18; Table 4, page 19
Table 7, page 26 Table 8, page 27
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Anaesthesia:
Figure 6, page 14
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Postgraduate Medical Journal:
Figure 2, page 7; Figure 5, page 13
Figure 7, page 15; Figure 1, page 59
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Introduction

Hans Selye reported the anaesthetic effect of steroids in 1941.[32] That discovery at McGill University Montreal, and Selye's subsequent explorations in the steroid field, opened the door to a potential new source of compounds of high anaesthetic activity and low toxicity. It was to steroids that Glaxo research groups turned their attention, with the aim of developing a product that would be a tangible advance in intravenous anaesthesia. The anaesthetic they have produced is Althesin (CT 1341).

Extensive human pharmacological studies and trials on Althesin (bibliography, page 68) have confirmed clinically the promising results of animal work. Althesin is a highly satisfactory induction agent and is valuable as the main anaesthetic for short procedures - because it has a notably wide margin of safety and little local irritancy, and gives prompt, smooth induction and rapid recovery normally free from 'hangover' effect. Studies in France and Japan with Althesin as the main anaesthetic for major surgery,[16, 36] draw into focus some of the chief characteristics of this new anaesthetic and suggest, in due course, an even wider range of usefulness.

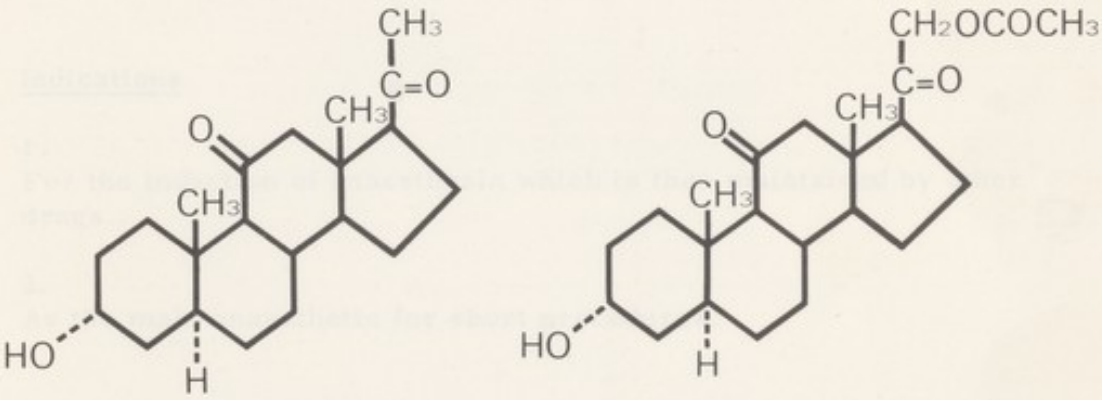
The numerous advantages that Althesin offers make it a distinct new aid for anaesthetic practice.

CHEMISTRY

During the development of Althesin many steroids were screened as potential intravenous anaesthetics. Glaxo research workers selected for further investigation the pregnane derivative, 3α-hydroxy-5α-pregnane-11,20-dione (later named alphaxalone), because of its high anaesthetic potency and rapid induction of anaesthesia in animals. The steroid proved to have a high therapeutic ratio (minimal anaesthetic dose compared with lethal dose for 50 per cent of mice), and to be virtually devoid of irritant effect at the site of injection. But alphaxalone was practically insoluble in water. A hundred-fold increase in solubility could be obtained by the use of a surfactant - an accepted method of solubilising oil-soluble substances, for injection. The surfactant chosen was a water-soluble polyoxyethylated castor oil.

The aqueous solution of alphaxalone so formed still did not contain sufficient of the steroid to make a convenient intravenous dose-volume. It was found that a closely-related steroid, the 21-acetoxy derivative of alphaxalone (subsequently named alphadolone acetate) had a co-solubilising effect which produced a more than three-fold increase in the solubility of alphaxalone. This additional solubility enabled 9 mg of alphaxalone to be brought into 1 ml of solution. The maximum solubility occurred when alphadolone acetate was present in the proportion one part to three of alphaxalone.

Figure 1



Alphaxalone

Alphadolone acetate

The mixture of steroids, together with the surfactant, was formulated into an injection (see formula on page 3) which was given the code number CT 1341 and afterwards named Althesin.

Althesin

Alphaxalone	0·90 G
Alphadolone acetate	0·30 G
Polyoxyethylated castor oil	20·00 G
Sodium chloride	0·25 G
Water for Injections	to 100 ml

Each millilitre of Althesin contains 9 mg of alphaxalone and 3 mg of alphadolone acetate.

Alphadolone acetate has anaesthetic properties similar to alphaxalone, but is half as potent: it is only included for its solubilising effect.

Althesin is a ready-to-use solution of small dose-volume, of pH about 7, isotonic with blood, for intravenous injection.

ANAESTHESIA WITH ALTHESIN (CT 1341)

The recommended dosage of Althesin is from 0·05 ml (50 microlitres) to 0·075 ml (75 microlitres) per kilogram body weight - which, for a patient of average weight (65 kg), is equivalent to 3·25 to 5·0 ml of the solution. Nevertheless a dosage of 0·20 ml/kg (four times the recommended minimal dose) has been given without serious side effects except for a period of apnoea requiring ventilation:[12] this wide safety margin is a clinical reflection of the high therapeutic ratio.[8]

Duration of anaesthesia is dose-dependent to some extent. After the recommended dose unconsciousness lasts for about five to ten minutes, surgical analgesia being present for about half that time; the initial dose may be supplemented if the anaesthesia needs to be prolonged.

Althesin should be injected slowly. Usually it is well tolerated and painless.

On induction the pupils commonly dilate, the eye-lash reflex disappears and muscle tone is reduced. There is usually a fall in blood pressure, which is not untoward, but cardiac output is generally maintained. In most patients after a few seconds of apnoea normal ventilation is restored. Transfer to inhalational anaesthesia is smooth.[37]

Recovery is progressive and rapid; postoperative nausea and vomiting are notably infrequent. Many observers have reported the high patient-acceptability of the anaesthetic and the pleasantness of recovery.[4, 12, 16]

Indications

1.
For the induction of anaesthesia which is then maintained by other drugs.

2.
As the main anaesthetic for short procedures.

Dosage and administration

A guide to the recommended dosage of Althesin for adults and children is given in the tables below.

Table 1

Adult dosage

Bodyweight		Dosage, 0·05ml*/kg	Dosage, 0·075ml+/kg
Kilograms	Pounds	Dose volume (millilitres)	Dose volume (millilitres)
50	110	2·5	3·7
55	121	2·7	4·1
60	132	3·0	4·5
65	143	3·2	4·9
70	154	3·5	5·2
75	165	3·7	5·6
80	176	4·0	6·0
85	187	4·2	6·4
90	198	4·5	6·7

* equivalent to 0·60 mg total steroids
+ equivalent to 0·90 mg total steroids

Table 2

Children's dosage

Bodyweight		Dosage, 0·05ml*/kg	Dosage, 0·075ml+/kg
Kilograms	Pounds	Dose volume (millilitres)	Dose volume (millilitres)
** 10	22	0·5	0·7
** 15	33	0·75	1·1
** 20	44	1·0	1·5
25	55	1·2	1·8
30	66	1·5	2·2
35	77	1·7	2·6
40	88	2·0	3·0
45	99	2·2	3·3
50	110	2·5	3·7

* equivalent to 0·60 mg total steroids
+ equivalent to 0·90 mg total steroids
** young children usually require the higher dosage (0·075ml/kg)

Dosage and administration

As with other anaesthetics, it is recommended that patients should fast before receiving Althesin.

For induction, the sleep dose should be given by slow intravenous injection (over 15 to 30 seconds). Supplementary dosage may be given at intervals if indicated by movement in response to surgical stimulation, or if further time is needed for the surgical procedure. The additional dose or doses may be equal to, or a fraction of, the initial volume given.[35]

Althesin appears not to prolong the action of neuromuscular blocking agents, and undue summation of effect with adjuvant drugs or other anaesthetics has not been seen.[3, 11, 18, 23]

Althesin does not require dilution. If desired it may be diluted with any solution isotonic with blood (Water for Injections may cause discomfort). The ready-to-use solution should be clear and free from crystals and, for convenience, should not be shaken as this may cause frothing.

Althesin does not contain antibacterial agents.

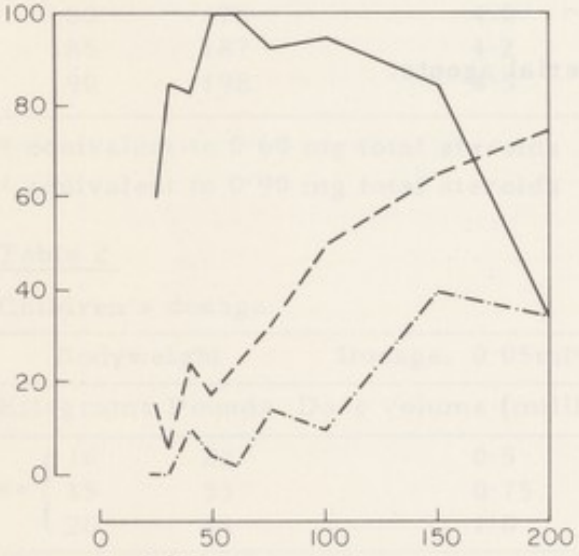
Side effects

Irritation to veins and tissues is minimal.

On induction the skin of the neck and upper chest may flush for a few minutes. Involuntary muscle movements may occur, the incidence increasing with dosage. These minor excitatory phenomena are seen more often when premedication is with hyoscine (scopolamine) alone. Hiccoughs may occur - less frequently than muscle movements - and do not usually interfere with anaesthesia or surgery (Figure 2).

Figure 2

Dose of Althesin, and incidence of hiccough, excitatory effects and acceptable induction.[11]



Acceptable induction_____
Excitatory effects (involuntary muscle movements)_ _ _ _ _ _ _
Hiccough_ . _ . _ . _ .

Acceptable induction defined as: smooth and uncomplicated; or with minor side effects not interfering with anaesthesia or surgery.

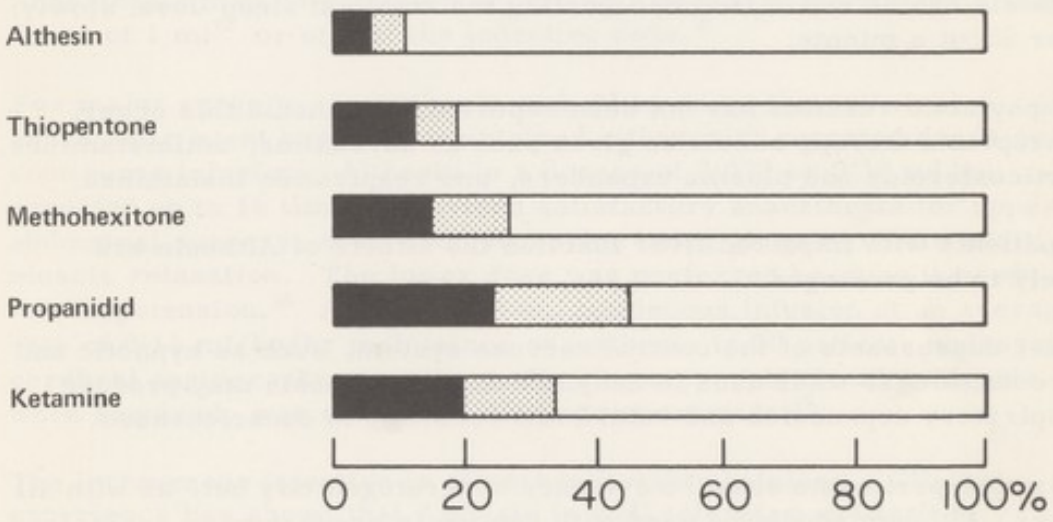
All patients were premedicated with atropine 0·6 mg.

Bronchospasm occasionally develops. Very infrequently generalised muscle movements have occurred. Laryngospasm is also extremely rare, but has been reported in association with marked salivation.[35]

During recovery, short periods of coughing, salivation, hiccoughing or shivering have been noted. In some patients crying and confusion occurred after out-patient dental surgery, but the apparent distress was 'perversely' contradicted by patient acceptance of 100 per cent and amnesia for the procedure was total.[38] Postoperative nausea and vomiting are notably infrequent (Figure 3).

Figure 3

Post anaesthetic vomiting and nausea.[12]



Percentage incidence of vomiting (black areas) and nausea (stippled areas) in the first six hours after approximately equipotent doses of five intravenous anaesthetics.

[Figures for anaesthetics other than Althesin from Dundee and Clarke (1964) and Knox et al (1970).]

98 minutes (the infusion being stopped 10 minutes before the end of the operation), 'the quality of recovery was remarkable for its rapidity, clear-headedness and degree of orientation with an underlying mood of euphoria.'[16]

Cumulation is not a feature of Althesin; for example, a patient who was given a total of 104 ml of Althesin by repeated doses for 5 hours 52 minutes, responded to verbal command after 48 minutes.[36] On the other hand, patients with severe hepatic insufficiency took from one to two hours to recover, following continuous infusion[16] - suggesting that the liver is the main site of inactivation of the steroids.

Effects on muscle

Muscle tone is considerably reduced by Althesin. The relaxation may allow the tongue to fall back, hence the jaw must be supported. Laryngeal and glottic reflexes are usually depressed but not obliterated. Visualisation of the larynx is good and endotracheal intubation has been performed using Althesin alone[16, 35] - however, that procedure is not advisable as coughing may be provoked. It is recommended that a muscle relaxant or topical analgesic be given before intubation. Good relaxation of the jaw muscles facilitates access to the mouth for surgery. Abdominal relaxation is adequate to allow easy palpation of the uterus.

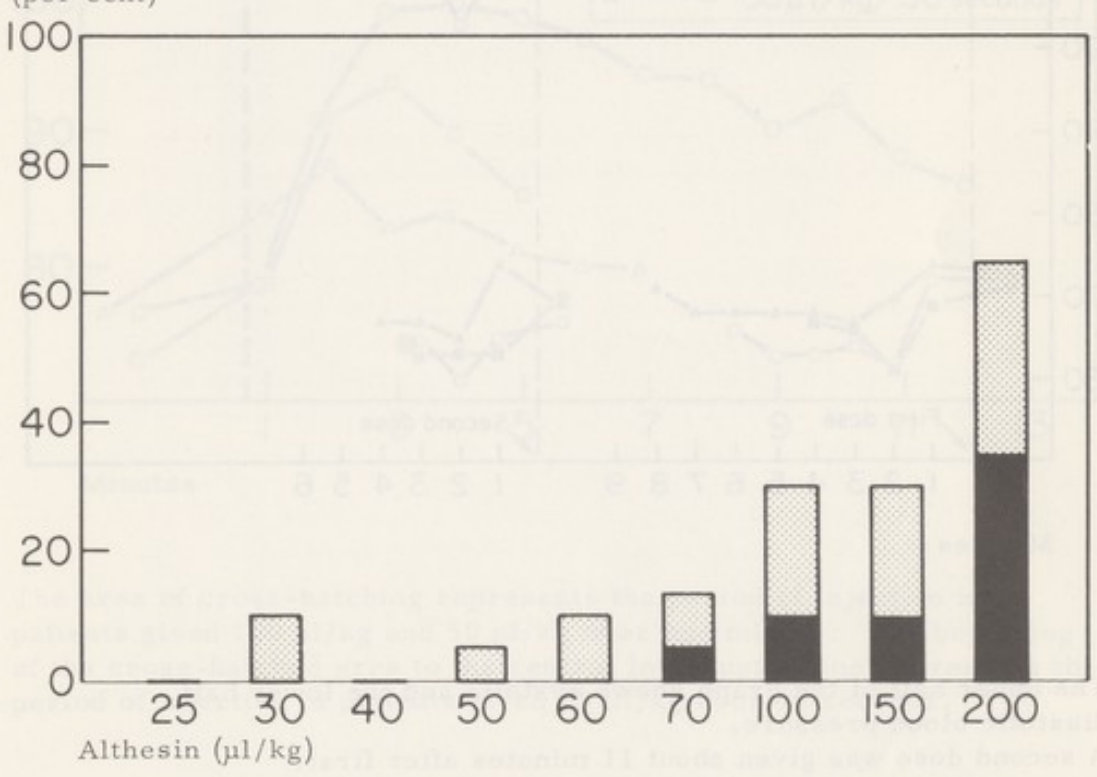
Occasionally excitatory phenomena (see page 7) may precede the relaxed phase. The dose, rate of injection and type of premedication probably have a bearing on the incidence of muscle irritability, but further investigation is necessary.[12]

Cardiovascular effects

Soon after injection of Althesin there is peripheral vasodilation, sometimes seen as a slight flushing of the skin, followed by a fall of central venous pressure, stroke volume and arterial blood pressure. Within about two minutes of injecting the recommended dose the fall in blood pressure, in normotensive patients, is commonly of the order of 10 to 20 per cent. Even with a dosage of 0·20 ml/kg there was no severe hypotension (fall of 60 mm Hg or more),[12] figure 4. Similar falls in blood pressure (Figure 5, page 13), central venous pressure, and stroke volume have been observed after induction with barbiturate anaesthetics in fit patients.[30]

Figure 4

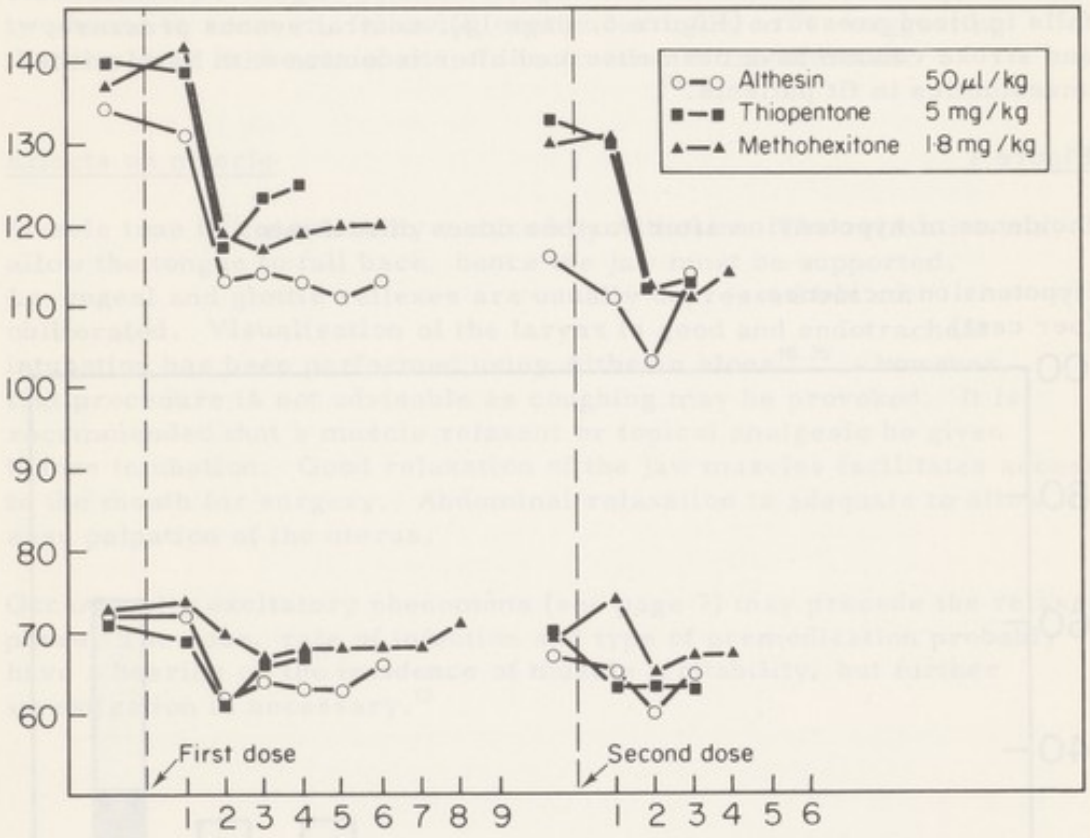
Incidence of hypotension after various doses of Althesin.[12]



Stippled areas represent falls of 20-40 mm Hg. Black areas, falls of between 40 and 60 mm Hg.

Figure 5

Changes in systolic and diastolic blood pressure following induction of anaesthesia with Althesin, thiopentone and methohexitone.[30]

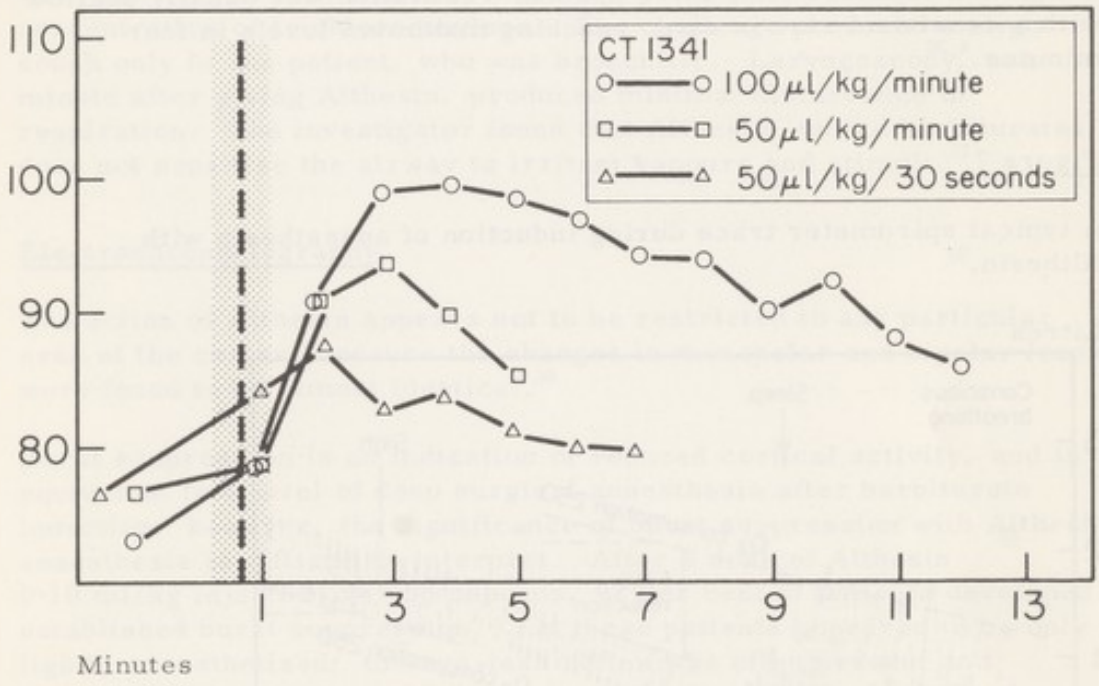


The upper half of the graph shows systolic and the lower half diastolic blood pressure.
A second dose was given about 11 minutes after first.

The heart rate increases by about 14 to 20 per cent (Figure 6). The tachycardia appears to compensate for the fall in stroke volume, and cardiac output is usually maintained or even increased, despite the initial drop in central venous pressure.[29]

Figure 6

Mean pulse rate in three groups of patients before and after induction with Althesin.[29]



The area of cross-hatching represents the period of injection in patients given 100 µl/kg and 50 µl/kg over one minute. The beginning of the cross-hatched area to the central interrupted line represents the period of injection in patients given 50 µl/kg over 30 seconds.

Electrocardiogram

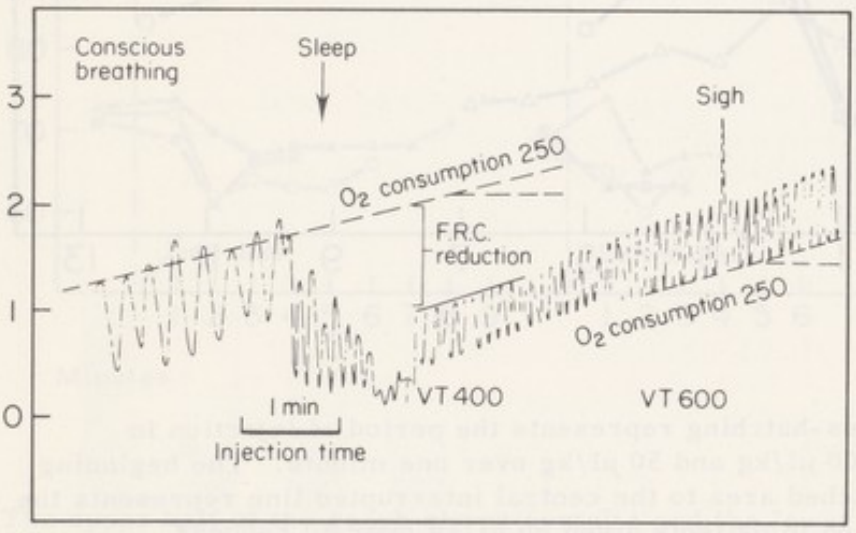
In several studies[4, 35, 38] where the electrocardiogram was monitored, no changes were reported.

Respiratory effects

Althesin produces very little disturbing effect on the respiratory mechanics or airway dynamics. One investigator[37] found that usually there is a small fall (about a litre) in the functional reserve capacity. After a brief period of apnoea respiration continued at a constant rate with a rapid return towards normal lung volume (Figure 7). Other observers reported that, after apnoea, ventilation was usually shallow with a consistent rise in rate, reaching maximum levels in four minutes.[4, 29]

Figure 7

A typical spirometer trace during induction of anaesthesia with Althesin.[37]



The patient, a 61-year-old female, was given 8 ml of Althesin.
FRC - functional reserve capacity.
VT - tidal volume.

Increase in lung compliance simplified intermittent positive pressure ventilation, and proved useful in asthmatic patients;[16] however, measurement of 'pressure volume loops' in another study[37] showed no changes in lung compliance.

With patients breathing air there is a moderate fall in arterial oxygen tension (PaO_2) from pre-induction levels, the tension gradually returning towards normal. $PaCO_2$ is slightly increased and there is a slight fall in pH.[4,29] Comparative studies have shown that similar changes occur with the barbiturate anaesthetics.[30]

To determine whether the respiratory endothelium is sensitised by Althesin, patients who had received 0·10 ml/kg of the induction agent were challenged with a sudden blast of 4 per cent halothane or a high concentration of trichloroethylene. The challenge produced a slight cough only in one patient, who was bronchitic. Laryngoscopy, one minute after giving Althesin, produced minimal disturbance of respiration. The investigator found that Althesin, unlike barbiturates, does not sensitise the airway to irritant vapours and stimuli.[37]

Electroencephalography

The action of Althesin appears not to be restricted to any particular area of the cortex, because the changes in monopolar and bipolar leads were found to be almost identical.[36]

Burst suppression is an indication of reduced cortical activity, and is equivalent to a level of deep surgical anaesthesia after barbiturate induction; however, the significance of burst suppression with Althesin anaesthesia is difficult to interpret. After a dose of Althesin 0·10 ml/kg injected over 60 seconds, 92 per cent of patients developed established burst suppression. Yet these patients appeared to be only lightly anaesthetised: the eye-lash reflex was often present and frequently there were small jerky movements of the limbs. On the other hand, of the patients who were given a smaller dose of Althesin, 0·05 ml/kg over 60 seconds, only 25 per cent reached a level of established burst suppression; nevertheless, clinically they were adequately anaesthetised.[29]

Metabolism

Protein binding of the steroid constituents is not extensive, alphaxalone being bound approximately 40 per cent, and alphadolone acetate about 30 per cent.[10]

The half-life of alphaxalone has not been established in man but, in various animal species including monkeys, it is between six and eight minutes - as estimated by gas-liquid chromatography (see page 23).

The prolonged recovery (one to two hours) in two patients with severe liver failure[16] accords with evidence from animal experiments that the liver is the main site of inactivation and elimination of the steroids (see page 23). Clincial experience also appears to confirm the autoradiographic studies[6] in rats which show (see page 23) that the steroids are not redistributed in the fat - progress to recovery from Althesin anaesthesia being steady, and usually free from hangover effect.

Effect on serum electrolyte and cortisol levels

Induction with Althesin 0·05 or 0·10 ml/kg has caused no significant changes of serum electrolyte or cortisol levels.[29]

Animal experiments have shown that Althesin is virtually devoid of hormonal effects (see page 24).

ANIMAL PHARMACOLOGY

Anaesthetic activity

Single doses

The anaesthetic activity of Althesin (CT 1341) in single doses was investigated in mice, rabbits, cats, dogs and monkeys (Table 3).

Table 3

Anaesthetic activity of Althesin in various animal species.[8]

Species	Intravenous dose (mg/kg)	Number dosed	Number sleeping	Duration of sleep (min)* Mean	SE	Number dying
Mouse	0·75	20	0	0		0
	1·5	20	20	0·5	0·04	0
	6·0	20	20	3	0·2	0
	24·0	20	20	11	0·6	0
	48·0	20	20	34	3·6	14
Rat	0·75	10	0	0		0
	1·5	10	10	2	0·2	0
	6·0	10	10	12	0·8	0
	24·0	10	10	35	3·1	1
	48·0	10	10	75	4·5	6
Rabbit	1·2	6	6	4	0·5	0
	3·6	6	6	13	1·1	0
	10·8	6	6	34	3·7	1
	21·6	6	6	-		6
Cat	0·36	3	2	1		0
	1·2	3	3	8	0·9	0
	3·6	3	3	22	1·5	0
	10·8	3	3	112	7·4	0
	32·4	3	3	-		3
Monkey	0·36	2	1	1		0
	1·2	2	2	6	1	0
	3·6	2	2	24	2	0
	10·8	2	2	30	6	0
	32·4	2	2	81		0
Dog	1·2	2	2	20	3	0
	3·6	2	2	71	10	0
	10·8	2	2	206	8	0
	32·4	2	2	302		1

*Duration of loss of 'righting reflex'. SE = standard error.

For mice and rats, Althesin was diluted with physiological saline.

Althesin proved to be more active than other commonly used induction anaesthetics and, in all species examined, produced rapid loss of consciousness at the lowest active doses. Recovery from the effects of non-lethal doses was rapid and uncomplicated in all animals except the dog (members of the genus Canis exhibit an 'idiosyncratic' response to polyoxyethylated castor oil and, therefore, the dog was not used for the investigation of major pharmacological actions of Althesin).

The therapeutic ratio, the dose required to kill 50 per cent of mice (LD50) compared with the dose required to produce loss of the 'righting reflex' in 50 per cent of mice (AD50), was determined for Althesin and some other anaesthetics (Table 4).

Table 4

Anaesthetic and lethal doses for 50 per cent of male CD† mice, of Althesin (CT 1341) and five other anaesthetics by intravenous injection.[8]

Anaesthetic	AD50 (mg/kg)		LD50 (mg/kg)		Therapeutic ratio (LD50/AD50)
Althesin	1·79	(1·57-1·96)*	54·7	(51·5-60·2)	30·6
Hydroxydione	18·0	(15·0-20·4)	311·0	(290·2-323·2)	17·3
Thiopentone	13·2	(10·3-15·1)	90·5	(87·4-94·1)	6·9
Methohexitone	5·35	(4·06-7·12)	39·4	(37·9-41·3)	7·4
Propanidid	22·9	(17·4-26·4)	184·7	(175·4-194·4)	8·1
Ketamine	12·7	(9·95-14·9)	108·3	(97·3-118·8)	8·5

† Charles River CD1 strain
* Fiducial limits; P = 0·05, 10 mice per group.

The fact that Althesin has a wide margin of safety has been confirmed in other species, including rats, guinea pigs, rabbits, monkeys and cats.

In the cat the depth of anaesthesia with different doses of Althesin was studied. A dose of 0·4 mg/kg produced immediate loss of righting reflex lasting for about one minute, with complete recovery from ataxia after about seven minutes. The depth and duration of effect increased as the dose was raised until with 3·6 mg/kg the corneal reflex was absent for three minutes. Surgical anaesthesia, sufficient to expose and cannulate blood vessels, was obtained for five to ten minutes with a dose of 7·2 mg/kg. Cats tolerated a dose of 19·2 mg/kg with only slight

depression of respiration, but 32·4 mg/kg caused apnoea, vascular collapse and death.

Repeated doses

The duration of loss of righting reflex in mice was measured after repeated doses of Althesin and other intravenous anaesthetics. The results are shown in table 5.

Table 5

Duration (minutes) of loss of 'righting reflex' in mice given repeated intravenous doses of five anaesthetics. The doses were repeated 30 seconds after the return of the 'righting reflex'.[14]

Dose*	Thiopentone 40mg/kg	Methohexitone 28mg/kg	Propanidid 100mg/kg	Ketamine 35mg/kg	Althesin 12mg/kg
First	5·7	4·9	2·5	5·8	6·5
Second	37	6·8	2·8	10·0	8·0
Third	101	10·4	3·4	13·1	8·1
Fourth	178 (1 died)	11·1	3·6	13·5	8·5
Fifth	>300	12·0	3·9	16·1	8·4
Sixth		12·8	3·4	14·3 (3 died)	8·4
Seventh		15·8	3·2	13·6	8·6
Eighth		15·2	3·1	19·2	8·5
Ninth		15·8	3·6	24·5 (1 died)	8·3
Tenth		17·3	3·4	23·0	9·9

* Doses for each drug were chosen to give an initial sleep time of about five minutes, but a dose of propanidid high enough to produce sleep beyond 2·5 minutes was lethal to some mice. Five mice were used in each group.

Infusions

In five fasted adult cats, which had been induced with Althesin 0·6 ml/kg and then intubated, prolonged anaesthesia was maintained by infusion

Althesin proved to be more active than other commonly used induction anaesthetics and, in all species examined, produced rapid loss of consciousness at the lowest active doses. Recovery from the effects of non-lethal doses was rapid and uncomplicated in all animals except the dog (members of the genus Canis exhibit an 'idiosyncratic' response to polyoxyethylated castor oil and, therefore, the dog was not used for the investigation of major pharmacological actions of Althesin).

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Second	37	6·8	2·8	10·0	8·0
Third	101	10·4	3·4	13·1	8·1
Fourth	178 (1 died)	11·1	3·6	13·5	8·5
Fifth	>300	12·0	3·9	16·1	8·4
Sixth		12·8	3·4	14·3 (3 died)	8·4
Seventh		15·8	3·2	13·6	8·6
Eighth		15·2	3·1	19·2	8·5
Ninth		15·8	3·6	24·5 (1 died)	8·3
Tenth		17·3	3·4	23·0	9·9

* Doses for each drug were chosen to give an initial sleep time of about five minutes, but a dose of propanidid high enough to produce sleep beyond 2·5 minutes was lethal to some mice. Five mice were used in each group.

Infusions

In five fasted adult cats, which had been induced with Althesin 0·6 ml/kg and then intubated, prolonged anaesthesia was maintained by infusion

of Althesin 0·02 ml/kg/min. When the infusion continued for up to four hours, the cats recovered rapidly. After six-hour infusion, recovery in two cats was prolonged and a third animal died (it had received a total dose of 7·68 ml/kg of Althesin). Death was preceded by progressive respiratory embarrassment and changes in the electrocardiogram characterised by depression of the ST segment and QRS inversion. The electrocardiogram was normal in the animals which survived and respiratory rate and minute volume remained satisfactory. Some hyperventilation lasting from one to two minutes occurred when the infusion was stopped.

Vascular irritancy

No vein damage has been encountered in any animal, irrespective of dosage. Deliberate intra-arterial injection of Althesin into the central artery of the rabbit ear, during occlusion of the marginal ear veins, produced no macroscopic arterial damage. After four days no necrotic areas were seen in the ears, and there was no congestion, haemorrhage, oedema or arterial damage on histological examination. The only consistent finding was a sparse round cell infiltration along the marginal ear veins, which may have resulted from the mechanical occlusion of these vessels for 15 minutes after injection.

In cats no thrombophlebitis or tissue damage was seen after accidental perivenous injection. The tails of mice given Althesin into the tail vein were indistinguishable from those injected with saline.

Respiratory and cardiovascular effects

The cardiovascular and respiratory effects of Althesin were studied in unpremedicated adult cats of either sex.[10a] The animals had been prepared at least four days previously with polyvinyl cannulae implanted in the right external jugular vein and descending aorta. With the cats in a quiet resting condition control values were recorded for 15 to 30 minutes for blood pressure, heart rate and respiration rate. Althesin was injected through the intravenous cannula at a rate of 0·05 ml/kg/second, and washed in with 1·5 ml saline at the same rate, with the cats unaware that the drug was being given.

The first dose of Althesin was 0·10 ml/kg - the minimum required to produce loss of righting reflex - and this dose was doubled every two or three days, up to 1·6 ml/kg. (Doses of 3·2 ml/kg were lethal.)

Respiratory effects

After Althesin 0·20 and 0·40 ml/kg the respiratory rate sometimes increased one to five minutes after injection. The changes were small and seldom exceeded the upper values observed in resting, conscious cats. After a dose of 0·80 ml/kg the respiration was regular and thoraco-abdominal; and all the cats continued to respire spontaneously after the maximum dose of 1·6 ml/kg. Three of the seven cats studied showed some alteration in the depth or rate of respiration, which became shallow, irregular, or slow for a few minutes after induction.

Cardiovascular effects

The immediate response to Althesin injection was similar after each dose level of drug and consisted of a transient tachycardia that usually preceded, and persisted during, a short-lasting fall in mean aortic blood pressure. At each dose level, half a minute after the start of injection, the increase in heart rate and fall in blood pressure were significantly different from resting control values. These changes were succeeded by recovery except after the maximum dose of Althesin 1·6 ml/kg, when mean aortic blood pressure continued to fall for one minute after injection - to 49 $\pm$ 3 mm Hg (57 per cent of control) - before beginning to recover.

Effects of vehicle

To ascertain whether the vehicle contributed to the observed cardiovascular effects, 1·6 ml/kg of vehicle was given (equivalent to the volume in the maximum dose of Althesin) and it produced in the conscious cat a significant rise in the mean aortic blood pressure, one to four minutes after injection. The heart rate increased as blood pressure returned towards normal. The changes may be related to the cats' awareness of the injection, which in this case was not followed by anaesthesia.

Electrocardiogram

The effect of induction of anaesthesia on the lead II electrocardiogram, aortic blood pressure and heart rate were monitored continuously in conscious, unrestrained cats. Althesin 9·6 mg/kg (0·8 ml/kg) caused a sinus tachycardia and fall in blood pressure, but no abnormalities were recorded in the ECG. The changes in the ECG wave forms that occurred were related solely to the increase in heart rate. Similar effects were observed in the same cats after injection of thiopentone 24 mg/kg, but induction of anaesthesia with propanidid 32 mg/kg caused irregularities in the pulse and dysrhythmias in the ECG in most of the animals.[15]

Metabolism

The metabolism and excretion of Althesin was studied in rats by two methods.[10] The plasma half-life of alphaxalone, after intravenous administration of Althesin, was approximately seven minutes when the steroid was assayed by gas-liquid chromatography (GLC). However, the half-life of plasma radio-activity after intravenous injection of Althesin containing tracer-labelled alphaxalone or alphadolone acetate was longer. The difference suggests that the tracer technique measures circulating metabolites, as well as unchanged steroid. GLC estimations showed that the plasma half-life of alphaxalone in mice and monkeys is also six to eight minutes.

The observation that Gunn rats, a strain deficient in the liver enzyme glucuronyl transferase, sleep for longer than do normal rats after receiving Althesin, indicates that glucuronide formation of the steroid components or of their metabolites is a likely route of metabolism and elimination of the anaesthetic.

After intravenous injection of Althesin containing labelled steroids into rats bearing implanted biliary cannulae, about 70 per cent of the radio-activity is excreted in the bile in the first three hours. Less than one per cent of the total radio-activity is present as free steroid, the bulk being in the form of highly polar conjugates. However, excretion is prolonged for up to five days - during which a total of 60 to 70 per cent of the radio-activity appears in the faeces and 20 to 30 per cent in the urine. The delayed excretion of the radio-activity may be the result of enterohepatic circulation of the steroid metabolites.

The results of preliminary experiments indicate that the major biliary metabolite of alphaxalone in the rat is a glucuronide of 2 α - hydroxyalphaxalone.

Protein binding

The steroid constituents of Althesin are protein bound in serum to between 20 and 40 per cent, depending on the animal species, alphaxalone showing the greater binding.

Tissue distribution

Autoradiography has been used in the rat to establish the distribution and possible sites of metabolism of alphaxalone and alphadolone acetate.[6] Two forms of radioactive Althesin were prepared, containing

either alphaxalone or alphadolone acetate labelled with ^{14}C in the 21 position. Male and 20-day pregnant rats were injected with the labelled preparations and killed at various times up to 60 minutes after dosing. Whole body autoradiographs were prepared and sections were also stained with haematoxylin and eosin, as an aid to indentification of labelled tissues.

The distribution and excretion patterns of the two labelled steroids were essentially the same. Initially the steroids became widely distributed in body tissues. Localisation in the central nervous system was apparent within one minute, and isotope was present in higher concentration in grey than in white matter. By ten minutes, loss of steroid from grey matter had reversed the relative concentrations. There was no evidence of any selective uptake by specific regions of the cortex or cerebellum.

Appreciable quantities of isotope were present in renal cortex at one minute, and renal clearance of alphaxalone and alphadolone acetate, or their metabolites, continued throughout the 60 minutes.

The highest concentration of isotope occurred in the liver, three minutes after injection; high concentrations were also present in the bile ducts and the lumen of the duodenum. By one hour isotope had been almost cleared from body tissues. Traces were present in liver, kidney, preputial gland and testis, but the bulk of the isotope was now in the lumen of the gut and bladder.

In the pregnant female the distribution of alphaxalone was similar to that in the male. Low concentrations of isotope, comparable with those in blood, were found in the placenta; in the foetus, the intestine was the only site in which the concentration exceeded that in maternal blood. Isotope was detected in foetal cerebral cortex three and ten minutes, but not thirty minutes, after dosing.

Both steroids appear to be rapidly removed from lipids, although alphaxalone and alphadolone acetate are lipid-soluble.

Hormonal effects

Althesin was found to be virtually devoid of hormonal effects when tested in mice, rats and rabbits.[9] The results are shown in table 6.

Table 6

Investigation of hormonal effects of Althesin.

Test and results	Conclusions
Thymus involution test in immature mice. No loss in thymus weight	No anti-inflammatory activity in mice
Uterine weight test in immature mice. No gain in weight	No oestrogenic activity in mice
Endometrial changes in oestrogen-primed female rabbits. No change	No progestational activity in rabbits
Weight change in levator ani muscle, preputial gland, seminal vesicle, or kidney in rats or mice. No weight gain	No androgenic or anabolic activity in rats or mice
Uterine weight test in oestrogen-primed mice. Small weight loss	Weak anti-oestrogenic activity in mice

Althesin did not affect urinary electrolyte excretion when given intravenously or subcutaneously to adrenalectomized rats. In terms of steroid content Althesin was found to have less than one twenty-fifth of the mineralocorticoid activity of desoxycorticosterone acetate (DOCA).

Pyrogenic tests
In cats no pyrexia was observed after Althesin had been given intramuscularly, intravenously or by infusion for six hours.

Althesin with inhalational anaesthetics

Six inhalational anaesthetics were given to unpremedicated cats induced with Althesin, the carrier gas being a nitrous oxide/oxygen mixture, except for the study with cyclopropane where oxygen alone was used. The results are summarised in table 7 (page 26).

Table 7

Effects of inhalational anaesthetics on cats induced with Althesin 0·60 ml/kg.[8]

Inhalational anaesthetic	Concentration (vols %)	No. of cats	Observations	
			During 50 minutes maintenance anaesthesia	During recovery period
Halothane	1·0	3	Respiratory minute volume depressed for a time after instituting maintenance. Progressive tachypnoea. Bradycardia in two cats	Hyperventilation on discontinuing anaesthetic. Rapid recovery.
Methoxyflurane	0·5-1·0	3	Smooth, uncomplicated maintenance of anaesthesia. Bradycardia in one cat	Hyperventilation on discontinuing anaesthetic. Fairly rapid, uncomplicated recovery
Chloroform	1·0-2·0	3	Marked tachypnoea in two cats, depression of respiratory minute volume in the other. Profuse salivation in one cat. Tachycardia and multifocal ventricular extrasystoles recorded in ECG of two cats; sinus arrhythmia in the other	Hyperventilation on discontinuing anaesthetic. Return to normal sinus rhythm after a few minutes. Fairly rapid recovery
Trichloroethylene	2·5	3	Respiratory minute volume depressed in the early period of maintenance. Progressive tachypnoea. Tachycardia and ventricular extrasystoles recorded in the ECG	Hyperventilation on discontinuing anaesthetic. Return to normal sinus rhythm after a few minutes. Protracted recovery. One cat exhibited nystagmus and salivated profusely
Diethyl ether	6·0	3	Profuse oral, nasal and bronchial secretions. Increased respiratory rate and minute volume. Tachycardia	Intense and protracted period of hyperventilation on discontinuing anaesthetic. Otherwise uncomplicated recovery
Cyclopropane	20·0-22·5	3	Depression of respiratory minute volume during maintenance period. Marked bradycardia in two cats	Short period of hyperventilation on discontinuing anaesthetic. Rapid recovery

The responses of the cats during maintenance, and the pattern of recovery from anaesthesia reflected the pharmacological properties of the inhalational anaesthetic employed. The prior administration of Althesin had no effect on the maintenance of anaesthesia or subsequent recovery, which was satisfactory in all animals.

Althesin with adjuvant drugs

(a) With Althesin given as a single dose
Fasted cats received Althesin 0·1 ml/kg (the minimal anaesthetic dose) or 0·6 ml/kg (a dose sufficient to produce surgical anaesthesia for about 15 minutes) one hour after treatment with an adjuvant drug.[8] The results are shown in table 8.

Table 8

The effect of adjuvant drugs on the course of Althesin anaesthesia in cats.[8]

Drug (given one hour before Althesin)	Dose* (mg/kg) and route	Effects of treatment	Effects on Althesin anaesthesia
Atropine sulphate +pethidine hydrochloride	1·0 im 7·5 im	Pupillary dilatation. Behaviour and gait affected	Return of corneal and flexor withdrawal reflexes slightly delayed
Chlorpromazine	5·0 im	Relaxation of nictitating membrane. Slight ataxia. Catatonic behaviour	No effects observed
Chlordiazepoxide hydrochloride	2·0 im	No effects observed.	No effects observed. Return of corneal and flexor withdrawal reflexes delayed. Emergence excitement in one cat
Papaveretum +hyoscine-N-butylbromide	2·0 im 0·5 im	Pupillary dilatation. Apprehensive behaviour. Salivation. Vomiting	
Quinalbarbitone sodium	10·0 po	Severe ataxia. Vomiting in one cat	Return of corneal and flexor withdrawal reflexes delayed. Recovery prolonged.
Methylpentynol	50·0 po	Vomiting in one cat. No other effects observed	No effects observed
Chloral hydrate	30·0 po	Drowsiness. Vomiting in one cat	No effects observed
Dihydrocodeine bitartrate	15·0 im	Pupillary dilatation. Salivation. Apprehensive, hyper-excitable behaviour	Return of corneal and flexor withdrawal reflexes slightly delayed
Pentazocine lactate	4·5 im	Pupillary dilatation. Apprehensive behaviour. Impairment of balance.	No effects observed
Promethazine hydrochloride	2·5 im	Slight pupillary dilatation	No effects observed

im = intramuscular po = per os *Three cats were used at each dose level

Electrocardiograms recorded during these investigations revealed no abnormality. In general the drugs had little effect on the course of anaesthesia or recovery seen when cats were given Althesin alone. Quinalbarbitone, which itself produced ataxia, delayed recovery from the anaesthetic but the cats recovered satisfactorily.

(b) With Althesin given as an infusion
Seven cats were anaesthetised with Althesin 0·6 ml/kg and anaesthesia was maintained by subsequent infusion at the rate of 0·02 ml/kg/minute.

The following drugs were then administered:
(i) Pethidine hydrochloride.
Doubling doses were given intravenously over the range 0·5 to 32 mg/kg at 20 minute intervals. After each administration there was a transient increase in heart rate and blood pressure, and a slight reduction in respiratory minute volume. One cat developed respiratory arrest after a second dose of pethidine 32 mg/kg, but recovered following artificial ventilation.

(ii) Morphine sulphate.
Small doses caused a slight fall in blood pressure and in the respiratory minute volume. At a dose of 2 to 4 mg/kg cardiorespiratory depression ensued.

(iii) Atropine sulphate.
A short lived, dose-related, fall in blood pressure was produced.

(iv) Pressor agents.
Characteristic elevation of blood pressure occurred after administration of metaraminol and methoxamine.

(v) Trimetaphan camsylate.
At 0·5 mg/kg a sustained fall of blood pressure and some bradycardia occurred.

(vi) Adrenergic blocking agents.
Phentolamine hydrochloride, given in two doses of 1 mg/kg, produced a reduction in the pressor response to adrenaline and noradrenaline. Propranolol hydrochloride, at a dose of 0·5 mg/kg, reduced blood pressure and heart rate; it also abolished the depressor effects of isoprenaline on the blood pressure. The pressor responses to adrenaline and noradrenaline were unaffected.

(vii) Bemigride.
Increasing doses caused progressive stimulation of respiration and lightening of anaesthesia.

The observations showed that, in these cats, the medicaments used could be combined safely with Althesin.

Althesin with neuromuscular blocking agents

One of three neuromuscular blocking drugs (suxamethonium chloride, gallamine triethiodide, tubocurarine chloride) was given with Althesin 0·60 ml/kg to cats premedicated with atropine and pethidine. Following intubation, anaesthesia was maintained with a mixture of halothane, nitrous oxide and oxygen until there was spontaneous respiration.

All the cats recovered satisfactorily. The neuromuscular blockade produced by suxamethonium was typically of the short duration depolarisation type and the effects wore off during the maintenance period with halothane. Gallamine and tubocurarine produced characteristic non-depolarisation block of longer duration.

Neurohumoral responses with Althesin

Cats anaesthetised with Althesin showed normal vascular reactions to acetylcholine, histamine, adrenaline and noradrenaline. However, when the cats received large cumulative doses of Althesin by infusion, the pressor response to adrenaline and noradrenaline was reduced to about 50 per cent, as was the tachycardia produced by adrenaline and isoprenaline. Partial recovery of these responses occurred when the rate of infusion was slowed.

ANIMAL TOXICITY

Short-term toxicity studies

The acute intravenous toxicity of Althesin and of the vehicle in mice and rats, and the acute toxicity of each steroid in male mice, are shown below.

Table 9

LD50 of Althesin and constituents.

	Mouse		Rat	
	Male	Female	Male	Female
Althesin (ml/kg)	3·13*	3·18	1·91	2·74
Vehicle (ml/kg)	37·2	35·3	5·1	5·7
Alphaxalone in vehicle (mg/kg)	30·9			
Alphadolone in vehicle (mg/kg)	86·5			

*Equivalent to 37·6 mg total steroids.

The animals which recovered showed no adverse effects, and tissues examined histologically showed no lesions attributable to treatment. The tail veins were not harmed by the injection.

The acute toxic effects of the steroids were solely additive.

Guinea pigs, rabbits and monkeys survived near-lethal single doses of Althesin and showed no ill effects. Histological examination of tissues from these animals and others given similar volumes of the vehicle revealed no lesions attributable to treatment.

Intra-arterial injections of Althesin into rabbits' ears caused no adverse effect, in marked contrast to the thrombophlebitis produced by 5 per cent solutions of sodium thiopentone.

Animal toxicity

Intermediate-term toxicity studies

Rats and cats were given once-daily intravenous injections of Althesin for seven consecutive days. Half the animals were killed 24 hours and the others 15 days after the last dose.

60 rats were given Althesin in daily dosages of 0·3, 0·6 or 1·2 ml/kg, and 24 cats received Althesin in daily dosages of 0·2, 0·6 or 1·8 ml/kg. Other groups were given volumes of saline or vehicle equal to the largest dosages of Althesin.

6 rats out of 20 given Althesin 1·2 ml/kg, 1 rat out of 20 given 0·6 ml/kg, and 1 cat out of 8 given 1·8 ml/kg, died. Anaesthesia lasted from 10 to 36 minutes in rats and from 10 to 140 minutes in cats.

No evidence of immediate or delayed specific toxicity of Althesin was discovered by microscopic examination of the major organs from male and female rats. Serum potassium concentrations of male rats given Althesin 0·6 or 1·2 ml/kg were reduced at the end of the observation period, although they had been within normal limits at the end of the treatment period. No other adverse effects of treatment were found in haematological studies, biochemical determinations on blood, serum and urine or body weight measurements carried out at intervals during the three week experiment. There was no thrombosis, phlebitis or other demonstrable ill effect on the tail veins after intravenous injection of Althesin or vehicle.

In cats, apart from the inevitable pulmonary complications of unpremedicated anaesthesia, no drug-induced haematological or biochemical changes were noted.

Long-term toxicity studies

40 rats and 16 cats were given once-daily injections of Althesin for a total of 21 doses. The rats received Althesin 0·3 ml/kg and the cats 0·2 ml/kg. Other groups of rats and cats were given equivalent volumes of saline or vehicle. Anaesthesia lasted from five to ten minutes in rats and about ten minutes in cats. During the experiment no cat died, but four male rats died from respiratory infection.

No specific toxic effects attributable to Althesin were detected. The spleens of male and female rats killed immediately after receiving Althesin or vehicle 0·3 ml/kg were much larger than those of rats given saline. The effect was reversible.

Effects on reproduction

The effect of Althesin on the fertility of male and female mice was investigated - particularly in view of its weak anti-oestrogenic activity. Before mating, these animals were dosed for 20 consecutive days with Althesin 0·5 ml/kg/day. No adverse effect on fertility was shown. A similar dose of Althesin given throughout pregnancy to mice produced no adverse effect on the pregnancy or progeny. Althesin, administered in near-lethal doses in the last five days of the gestation period of mice and rats, did not produce abortion or affect survival rate, litter size or the sex or fertility of the offspring.

Althesin appeared to be an acceptable anaesthetic in pregnant mice and rats, having no toxic effects on the mother or on the young.

Teratogenicity

Studies in mice and rabbits showed that Althesin had no teratogenic effects in these animals.

Groups of mice and rabbits were given daily intravenous Althesin, saline or vehicle during pregnancy. Doses of Althesin 0·5, 1·0, 2·0 or 3·0 ml/kg per day, were administered to the mice from day seven to day sixteen of pregnancy. Some mice that had received the largest dose did not recover from anaesthesia, but no adverse effects were noted in those that survived, nor in their progeny. Dutch rabbits were given dosages of Althesin 0·25, 0·50, or 0·75 ml/kg/day, from day eight to day sixteen of pregnancy. Some of the rabbits given 0·75 ml/kg died during anaesthesia, but no adverse effects were found in the surviving does, and their offspring were healthy.

STORAGE AND PRESENTATION

Storage

Althesin should be stored at room temperature - it should not be refrigerated as the steroids may crystallise out from solution and they are difficult to re-solubilise. The preparation should be protected from light.

Presentation

Althesin is presented in ceramically-printed ring-snap ampoules of 5 ml and 10 ml, in boxes of ten.

Each millilitre of Althesin contains 12 mg (1·2 per cent w/v) of total steroids, composed of 9 mg alphaxalone and 3 mg alphadolone acetate. The aqueous vehicle contains 20 per cent of a polyoxyethylated castor oil (a surfactant); the solution is rendered isotonic, with sodium chloride.

CLINICAL EXPERIENCE

Abstracts

A Preliminary Clinical Study of CT 1341 - A Steroid Anaesthetic Agent

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British Journal of Anaesthesia, 1971, 43, 14

Eight patients undergoing short superficial procedures were given CT 1341 (Althesin) to ascertain whether this anaesthetic was as effective in man as in animals, to determine an approximate dose range and to discover whether any obviously undesirable side effects followed.

The patients were unpremedicated and most of them received Althesin 0·10 ml/kg injected over 15 seconds. Anaesthesia was maintained with nitrous oxide and oxygen in a 70/30 mixture and, in two patients, further supplemented with trichloroethylene. Two patients breathed air only throughout the procedure. All surgical procedures were uneventful with the exception of troublesome muscle movement and possible muscle tremor in two cases. The range of induction time was 30 to 80 seconds and recovery time to response to command, 15 to 360 seconds. Seven patients exhibited a degree of euphoria on recovery. There was no evidence of respiratory depression, apnoea was not observed but tachypnoea was common.

The glottic and laryngeal reflexes were depressed immediately following induction but recovered quickly. No patient experienced laryngospasm or bronchospasm. All patients showed apparent peripheral vasodilation and a rise in pulse rate. The increase in systolic blood pressure, measured at four-minute intervals, was just statistically significant. No electrocardiographic abnormalities were noted.

Muscle hypertonia, limb tremors and nystagmus were not observed. The nasopharyngeal temperature was normal in all cases. There was no sign of local irritation and no thrombosis or phlebitis.

In a further group of six unpremedicated patients haemodynamic effects of CT 1341 were studied during diagnostic right and left heart catheterization. The dosage was 0·1 ml/kg, which was found to be on the low side as patient movement on stimulation was common. There was a significant rise in heart rate which was maximal two minutes after injection. Subsequent values, at 10 and 15 minutes, returned towards baseline measurements. A consistent though variable fall in systolic and diastolic blood pressures occurred after induction. Recovery was associated with a rise in blood pressure not significantly higher than baseline measurements. The duration of anaesthesia was 20 to 30 minutes.

There was no significant change in pulmonary artery pressure although individual variation occurred, and no significant change in mean cardiac output. A slight fall in stroke volume and a fall in systemic vascular resistance was noted in five out of six patients. In all patients the arterial oxygen tension (PaO_2) was reduced at one minute after injection, during anaesthesia, and during the early recovery phase. This fall in PaO_2 was highly significant. The fall in pH at each stage was also significant. Arterial carbon dioxide tension ($PaCO_2$) tended to rise but this change was not statistically significant. In every case there was a rise in respiratory rate following induction and apnoea was not observed. Pupils dilated following induction, and remained so until the patient had almost recovered. There was no evidence of phlebitis and no nausea or vomiting. Recovery was rapid and the patients were pleasantly euphoric without being restless.

The third group of six patients undergoing minor surgical procedures - who conformed to AMA Classification 1 criteria - was studied with particular reference to speed of recovery. No premedication was given. At the dose level of 0·15 ml/kg stable anaesthesia was obtained, although mild muscle movement in response to stimulation was observed in three cases. There was a highly significant increase in respiratory rate; all patients recovered with euphoria, and there were no signs of local irritation.

Induction, maintenance and recovery were relatively trouble-free and this new steroid agent seemed worthy of further clinical trial.

Clinical Studies of Induction Agents XXXIX: CT 1341, A New Steroid Anaesthetic

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Three hundred patients undergoing minor gynaecological surgery were admitted to a study to determine the optimum dose of CT 1341 (Althesin) as an induction agent. Patients were premedicated with atropine 0·6 mg intramuscularly, a predetermined dose of CT 1341 was given intravenously (Table 1) and anaesthesia maintained by 75 per cent nitrous oxide in oxygen. If deeper anaesthesia was required, supplemental doses of CT 1341, usually of 1 ml, were given.

Table 1

Number of patients studied in different dosage groups.

Dose (µl/kg)	Number of patients	Average age (years)	Average weight (kg)	Duration of anaesthesia (minutes)
25	20	29	64	7·0
30	20	35	61	11·2
40	50	32	60	6·5
50	50	32	60	9·7
60	50	35	56	8·7
75	50	34	61	8·5
100	20	37	60	11·2
150	20	33	55	11·0
200	20	29	55	8·1

Patients lost consciousness within one arm-brain circulation time when the dosage was adequate; 30 per cent of the patients who received 25 µl/kg and 20 per cent of those given 30 µl/kg failed to become unconscious.

The incidence of excitatory side effects was strongly correlated with dose (minimum 5 per cent, maximum 75 per cent). Hiccoughs were infrequent and less closely correlated with dose. Respiratory depression which required ventilatory assistance occurred only with the 200 µl/kg dose. Fall in blood pressure was insignificant in the dosage range 25 to 70 µl/kg. Above a 70 µl/kg dose significant hypotension sometimes occurred, and the incidence increased with the dose; but even with 200 µl/kg there was no severe fall (60 mm Hg).

The results indicated that the optimum range was 50 to 60 µl/kg almost three-quarters of the cases having completely smooth induction; above 100 µl/kg, the proportion was less than one-quarter. However the range 40 to 100 µl/kg was 'quite acceptable' for most cases.

The recovery after different doses of CT 1341 was assessed by the proportion of patients who were 'awake', 'safe', or 'unsafe' two minutes after termination of nitrous oxide. The largest number awake occurred in the 40 to 60 µl/kg range. Anaesthesia with CT 1341 was followed by remarkably little nausea (7 per cent) or vomiting (5 per cent).

The authors commented: 'the new steroid anaesthetic CT 1341 appears to be a satisfactory induction agent in the dose range 40 to 100 µl/kg. Induction is rapid with only minor excitatory effects and hypotension'.

CT 1341: some effects in man
Cardiorespiratory, electroencephalographic and biochemical measurements

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Anaesthesia, 1971, 26, No.4, 402

Measurements of the cardiorespiratory effects of CT 1341 (Althesin) were undertaken in 23 fit, unpremedicated patients undergoing surgery. Electroencephalographic (EEG) changes and biochemical effects were also studied. Arterial and venous cannulae were inserted for the measurement of blood pressure, central venous pressure (CVP) and cardiac output. Two standard dosages based on observations from animal studies were used and, with the lower dosage, two rates of injection were employed (Table 1).

Table 1

Dose of CT 1341 (Althesin) and rate of injection.

	Number of patients	Mean age	Mean weight (kg)	Dose of CT 1341 (µl/kg)	Time taken for injection (seconds)
Group 1	11	44	60	100	60
Group 2	6	42	58	50	30
Group 3	6	31	65	50	60

Following cannulation, the patients were allowed to settle for 15 to 30 minutes, CT 1341 was then injected and observations were continued until the patients awoke or until movement became excessive. Some of the patients then received a second dose (Table 2).

Table 2

Maximum changes in blood pressure, pulse rate and respiratory rate following injection of CT 1341 (Althesin).

	Fall in blood pressure (per cent)	Increase in pulse rate (per cent)	Increase in respiratory rate (per cent)
Group 1	Systolic 26 (3) Diastolic 18 (3)	37 (4)	53 (4)
Group 2	Systolic 20 (4) Diastolic 15 (4)	14 (2)	38 (4)
Group 3	Systolic 16 (4) Diastolic 12 (3)	22 (3)	31 (4)

Time (minutes) after injection is in parenthesis

In all groups the blood pressure gradually rose after the initial fall but never reached pre-induction levels. In all groups there was a fall in CVP which followed a similar pattern to the fall in blood pressure. The largest fall occurred in group 1.

In the five patients in group 1 where cardiac output was measured, output was well sustained and showed a tendency to increase. No dysrhythmias in electrocardiograms were seen.

Patients breathed air throughout the procedure. There was usually some irregularity of ventilation. In 60 per cent of the patients apnoea occurred shortly (74 seconds $\pm$ 25) after induction and was often preceded by a sigh or a few deep breaths. This period of apnoea was brief (mean 29 seconds $\pm$ 16) and was longest in group 1 (mean 35 seconds $\pm$ 27). Thereafter ventilation was usually shallow with a consistent rise in rate, maximum levels being reached within four minutes.

In group 1 post-induction blood gases were measured at three, eight and fifteen minutes. In groups 2 and 3 measurements were made at

three and six minutes only, because recovery was more rapid. In all three groups there was a slight rise in arterial carbon dioxide tension and a moderate fall in arterial oxygen tension.

Comparison between the times in seconds to specified EEG levels shows that 10 out of 11 patients reached established burst suppression at the larger dose (group 1) while only three of the twelve did so at the smaller dose (groups 2 and 3). No marked changes in biochemistry were seen.

When the polyoxyethylated castor oil solubilising agent in CT 1341 was given to man in doses comparable to those used at induction with CT 1341 there were no significant changes in blood pressure, pulse rate or CVP.

A Trial of CT 1341

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CT 1341 (Althesin) was used as the sole anaesthetic agent in a series of 109 patients; in a further 44 patients it was supplemented with nitrous oxide and oxygen. The patients' ages ranged from six to 80 years, and weight from 22 to 109 kg.

Dosage for induction was 'to some extent exploratory' - from 0·04 to 0·12 ml/kg. Muscle relaxants were not needed for the patients in these studies.

When manipulation or a brief surgical procedure was performed a single dose of Althesin sufficed. For more prolonged surgery, supplementary dosage was administered, usually half the initial dose but, when required very close to the end of surgery, a quarter. Nineteen of the 109 patients received atropine 0·6 mg, with morphine 10 mg or pethidine 100 mg, as pre-anaesthetic medication.

In 44 cases, where the surgery was expected to be long, Althesin injection was followed by nitrous oxide/oxygen mixture throughout the anaesthesia. Further doses of Althesin were administered later if required. Eighteen of these patients received premedication.

Althesin produced sleep in one arm-brain circulation time; the pupils commonly dilated; there was usually good jaw relaxation and patency of the airway was impaired. Three patients were intubated after injection of Althesin 0·08 or 0·10 ml/kg without muscle relaxant but, as there was coughing on the tube, the authors consider that a topical analgesic should be used for intubation. The average duration of surgery was 4·1 minutes (from 15 seconds to 28 minutes). Of the 85 patients who received a single dose of Althesin, anaesthesia was

satisfactory in 63; in 15 there was some movement in response to stimulation, and in the remaining seven patients surgery produced considerable reflex response.

The average time for the operations performed under Althesin supplemented by nitrous oxide and oxygen was nine minutes (three to 43 minutes).

Recovery was usually smooth and uneventful. Jaw tone and reflexes returned early. Recovery differed somewhat from that following barbiturates or propanidid - as return of consciousness and orientation was much slower. Nevertheless Althesin seemed to be inactivated fairly rapidly, and the time to full recovery and ambulation was of the same order as with other types of intravenous anaesthetic agents.

One minute after commencement of injection blood pressure fell (5 to 30 per cent), pulse rate rose (10 to 48 per cent), and respiration rate increased (3 to 50 per cent). The circulatory changes returned to normal levels within a short time but rapid respiration was maintained in some patients.

Irritation of the veins or tissues near the injection site was not seen; incidence of nausea and vomiting was 'very low', emetic symptoms occurring in only one of the 109 patients who received Althesin alone.

The incidence of excitatory phenomena was higher in the patients who had no premedication. During induction hiccough occurred in 12 patients, but was usually transient and did not interfere with anaesthesia or surgery, cough occurred in nine patients. Muscle movements were seen in some patients shortly after induction, but these did not usually interfere with the procedure. In a few patients surgical stimulation evoked a convulsive response.

In two patients an erythematous rash developed on the neck and upper chest shortly after induction. Six patients exhibited marked shivering during recovery. In four patients there was marked salivation and one of them developed laryngeal spasm.

Four patients were not included in the series because Althesin plus

nitrous oxide did not produce satisfactory anaesthesia, and a volatile supplement had to be added.

The authors conclude that the drug was sufficiently promising to justify further clinical trials to determine its value, especially in relation to the intravenous induction of general anaesthesia.

Althesin and hydroxydione: comparative laboratory and clinical investigations

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Postgraduate Medical Journal, 1972, June supplement, 120

Electroencephalographic changes in a preliminary cross-over study in twelve rabbits showed that Althesin was more potent and had a more rapid and a shorter duration of anaesthesia than hydroxydione.

These findings were reflected in a clinical study of 30 patients - 14 males and 16 females, ranging in age from 17 to 58 years - who were scheduled for abdominal surgery lasting not longer than 30 minutes. Meperidine 100 mg and atropine 0·5 mg were given subcutaneously 60 minutes prior to induction of anaesthesia. Althesin 0·2 ml/kg was injected as a single dose intravenously. Hydroxydione 15 mg/kg was diluted in 0·5 per cent Ringer's solution and administered as an intravenous infusion over 10 minutes. Anaesthesia was maintained in all patients with a 70:30 nitrous oxide/oxygen mixture.

The patients were divided into three groups of 10 patients each as follows:

Group 1 Althesin, breathing spontaneously
Group 2 Althesin, with assisted or controlled ventilation (following intubation)
Group 3 Hydroxydione, breathing spontaneously

Suxamethonium and alcuronium chloride were given as muscle relaxants to patients in group 2.

In groups 1 and 2 blood pressure (systolic and diastolic), heart rate and also PO_2, PCO_2, bicarbonate and pH were measured immediately before induction, five minutes after induction and after the end of

anaesthesia. It was considered unnecessary to take these measurements in the hydroxydione group. The blood sugar was estimated in all three groups, but the third sample was taken one hour after completion of the anaesthetic procedure, as any tendency for the level to rise becomes more evident at this time. The results were analysed statistically.

Systolic blood pressure in group 2 fell significantly five minutes after induction, but not in group 1. However, the heart rate increased significantly in group 1 but not in group 2.

PO_2 rose significantly in groups 1 and 2 following induction. After the end of anaesthesia CO_2 tension rose significantly in group 2 only. Five minutes after induction the pH was significantly lower in group 1 than in group 2. During anaesthesia there were no further significant changes in the pH in group 1, but in group 2 the pH fell significantly to 7·335.

Blood-sugar levels were not raised until one hour after the end of anaesthesia, when significant hyperglycaemia was present in the patients who received hydroxydione (group 3) or Althesin plus suxamethonium (group 2). In group 1 the blood-sugar levels rose slightly (6·1 per cent). The authors suggest that the hyperglycaemia in group 2 may have been caused by suxamethonium.

There was no gastro-intestinal disturbance and no thrombophlebitis, with either drug.

The clinical investigation showed that Althesin has a rapid onset of action and a quick recovery, in contrast to hydroxydione. However, both drugs gave satisfactory analgesia but poor relaxation - inadequate for abdominal surgery.

Althesin:
further studies of interaction with anaesthetic agents

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Postgraduate Medical Journal, 1972, June supplement, 123

A study of the effect of atropine premedication on Althesin anaesthesia is the first of two investigations.

Eighteen fit patients undergoing minor gynaecological procedures were allocated at random into three groups of six. Base line measurements of pulse rate and systolic blood pressure were made. Premedication consisting of either 2 ml isotonic saline (group 1, control), atropine sulphate 0·01 mg/kg bodyweight (group 2), or atropine sulphate 0·02 mg/kg (group 3), was then given.

Pulse rate and systolic blood pressure measurements were repeated at one-minute intervals for five minutes. An injection of Althesin (mean dose 50 to 60 µl/kg) was given intravenously over 60 seconds, supplemented by a mixture of 30 per cent oxygen with 70 per cent nitrous oxide. Measurements of pulse rate and systolic blood pressure were then repeated every minute for five minutes - before transfer to the operating theatre.

After premedication, heart rate increased and systolic blood pressure rose 8 per cent in group 2 and 11 per cent in group 3; subsequent injection of Althesin produced a further slight rise in the patients on atropine 0·01 mg/kg, but a slight fall in those on 0·02 mg/kg. After Althesin, systolic pressure fell in all patients, 15 per cent in the control group and in the group on the lower dose of atropine, and 20 per cent in the patients who had the higher dose of atropine.

The authors suggest that atropine premedication in patients undergoing Althesin anaesthesia should be at the lower dosage (0·01 mg/kg). When hyoscine is used an equipotent dosage would apply.

In the second investigation the possibility of adverse interaction between Althesin and methoxyflurane was examined in twelve patients. The patients received 10 mg papaveretum, 0·4 mg hyoscine, and 0·1 mg/kg of pancuronium and were anaesthetised with Althesin 50 µl/kg. The surgical procedures were mainly abdominal and anaesthesia was maintained with nitrous oxide and oxygen and an infusion of Althesin at a mean rate of 0·004 ml/kg/min. When anaesthesia was judged to be stable, 0·5 per cent methoxyflurane was introduced to the circuit for 20 minutes.

During infusion of Althesin there had been a highly significant rise in heart rate ($P<0·01$) and a significant rise in systolic blood pressure ($P<0·05$). When methoxyflurane was added there was no significant change in heart rate, but there was a highly significant fall in systolic blood pressure ($P<0·01$). There was no case of sinus tachycardia, although in one case wandering pacemaker developed during the introduction of methoxyflurane. Nasopharyngeal temperature did not vary in any patient.

Consistent interaction between Althesin and methoxyflurane was not established.

Group trial of Althesin as an intravenous anaesthetic

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Postgraduate Medical Journal, 1972, June supplement, 108

Results are presented of 800 administrations of Althesin - the first part of a group trial in Northern Ireland, in which 10 consultants, six senior registrars, three registrars and one senior house officer participated. Each anaesthetist was requested to use the drug for 40 cases in his routine clinical practice and to answer a questionnaire. Choice of premedication was left to the anaesthetist. Thirty-four of the cases were children under 10 years of age; of the 800 administrations (Table 1), 64 were to out-patients.

Table 1

Analysis of procedures included in the trial.

Procedure	Minor	Major	Total
General surgery	68	134	202
Gynaecological surgery	285	42	327
Cardiothoracic surgery	49	15	64
Dental surgery	3	36	39
Plastic surgery	12	24	36
Ophthalmic and ENT surgery	7	36	43
Neurosurgery	-	-	1
Obstetrics	-	-	10
ECT 51/Narcohypnosis 27	-	-	78

534 administrations (66·75 per cent) were trouble free. With a further 227 patients (28·38 per cent) induction was acceptable, with only minor upsets which did not interfere with anaesthesia or surgery. Upset which interfered with anaesthesia and delayed surgery, occurred in 37 cases (4·63 per cent). Serious side effects were seen in 2 cases

(0·25 per cent); in one prolonged respiratory depression; in the other a fall in blood pressure of 40 mm Hg for more than five minutes. Spontaneous muscle movement occurred in approximately 15 per cent of patients, but few of the anaesthetists considered muscle movement as being troublesome or potentially dangerous. The opinion of the 20 anaesthetists on the merits of Althesin are shown in Table 2.

Table 2

Opinion of 20 anaesthetists on the merits of Althesin compared with thiopentone, methohexitone and propanidid.

Criterion for comparison	Althesin compared with	Althesin considered to be: better	not different	slightly worse	much worse
Smoothness of induction	Thiopentone	5	8	7	0
	Methohexitone	16	3	1	0
	Propanidid	11	8	1	0
Excitatory phenomena	Thiopentone	3	5	11	1
	Methohexitone	16	3	1	0
	Propanidid	4	11	4	1
Ease of administration	Thiopentone	9	7	4	0
	Methohexitone	5	12	3	0
	Propanidid	16	4	0	0
Cardiovascular depression	Thiopentone	9	9	2	0
	Methohexitone	2	13	5	0
	Propanidid	9	8	3	0
Respiratory depression	Thiopentone	13	7	0	0
	Methohexitone	6	13	1	0
	Propanidid	7	8	5	0
Duration of recovery	Thiopentone	17	3	0	0
	Methohexitone	9	9	2	0
	Propanidid	0	7	10	3
Nature of recovery	Thiopentone	12	7	1	0
	Methohexitone	10	8	2	0
	Propanidid	2	13	5	0

The effects in man of infusions of Althesin with particular regard to the cardiovascular system

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Postgraduate Medical Journal, 1972, June supplement, 72

Althesin by intravenous infusion was used as the main anaesthetic in 70 patients undergoing neuro-radiological or orthopaedic procedures. Where limb movements indicated insufficient analgesia, supplements of analgesics were given. Premedication was kept to a minimum, most patients receiving atropine 0·5 mg alone; eleven cases had atropine and sedatives one hour before induction.

Induction of anaesthesia was achieved with 0·07 to 0·10 ml/kg (mean 0·074). Succinylcholine was given to facilitate intubation in nine cases and two cases received a longer-acting muscle relaxant to provide better orthopaedic operating conditions. The induction dose itself produced profound narcosis in about 40 seconds, usually characterised by myosis, centrally fixed eyes and a suppressed corneal reflex. Depending on the dose used anaesthesia generally lasted 8 to 12 minutes if no infusion was begun.

Infusion was maintained at an average rate equivalent to 0·11 ml undiluted Althesin/kg/hour, the solutions being made by adding 10 ml of Althesin to 200 ml of normal saline. In patients of average weight Althesin 10 ml by infusion provided anaesthesia for more than an hour. The analgesic effect was insufficient for surgery and was supplemented by giving repeated doses as required of dextromoramide or pethidine. Though this regimen depressed respiration, it did not prevent most patients breathing oxygen-enriched air spontaneously and effectively.

In most patients recovery from the anaesthetic was remarkably rapid and clear-headed - the rapidity being partly due to stopping the infusion 10 minutes before the completion of the operation. Postoperative nausea and vomiting was rare; the injection of Althesin was painless and venous

irritation was not seen. In three patients recovery was prolonged; two cases had severe hepatic insufficiency and one had been given a large dose of diazepam as premedication. Six patients experienced some agitation and confusion during recovery. Three were epileptics, one had a cerebral tumour, one a meningeal haemorrhage and one post-traumatic blindness. In all orthopaedic patients recovery was tranquil.

Hypotension between 10 and 30 mm Hg was produced in 45 per cent of normotensive patients, but in 18 of 20 hypertensive cases there was a 10 to 50 mm Hg fall of blood pressure. The hypotension produced by Althesin is accompanied by peripheral vasodilation and so it appears that the fall in blood pressure is not due to reduced cardiac output. The author suggests that, despite the apparent peripheral origin of the hypotension, Althesin may be contra-indicated in severely hypertensive and hypovolaemic states.

Respirometry and blood gas studies showed that Althesin reduces the tidal volume. Apnoea does occur though it is not preceded by bradypnoea. The giving of analgesics during Althesin anaesthesia did not increase respiratory depression. The increase of lung compliance was useful in several asthmatic patients.

The author concludes: 'this preliminary study shows Althesin to have several interesting new properties. It has a rapid onset of effect and provides useful anaesthesia of short duration'.

A comparison of recovery times between Althesin and methohexitone following anaesthesia for electro-convulsive therapy

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Postgraduate Medical Journal, 1972, June supplement, 112

Patients who were to undergo electro-convulsive therapy were chosen for a study to compare the recovery times after Althesin or methohexitone anaesthesia, as such cases allowed a within-patient comparison.

135 patients, 48 males and 87 females, whose ages ranged from 19 to 85 years, received two or more treatments using each induction agent. The time from start of injection of Althesin to return of eye-lash reflex was 309 seconds, and the comparable time for methohexitone, 251 seconds.

Atropine sulphate 1·2 mg was given intramuscularly one hour before treatment, or atropine sulphate 0·6 mg intravenously immediately before induction. Occasionally sedative premedication was required. The anaesthetics were given in a standard dose for light anaesthesia, Althesin 2·5 ml or methohexitone 50 mg, intravenously. The induction drug was followed by a standard dose of suxamethonium chloride, 25 mg intravenously. Shock was administered, care being taken to ensure that the same shock wave form and the same electrode placement (unilateral or bilateral) were given at all treatments for each patient. Violent facial flushing was noted in one patient after both Althesin and methohexitone: since this response also occurred following propanidid, it was assumed to be an individual phenomenon. Three patients exhibited prolonged convulsions after ECT following Althesin, but it was impossible to ascertain whether these were due to the drug or the mechanics of ECT shocks.

There was no significant difference in the incidence of hiccoughs.

The time from start of injection of each induction agent to the first breath (apnoea time) was also measured, to explore the possibility of interaction of suxamethonium with Althesin or methohexitone. The duration of apnoea with Althesin was 215 seconds and with methohexitone 206 seconds. Clinically there appeared to be no difference between the combination of suxamethonium and either of the induction agents.

Comparative recovery rates following induction of anaesthesia with Althesin and methohexitone in out-patients

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Postgraduate Medical Journal, 1972, June supplement, 116

The degree of recovery from anaesthesia induced by Althesin and methohexitone was assessed, at two set times, by measuring the degree of ocular divergence with a newly designed instrument - more sensitive than previous models.

The observations were conducted in a consecutive series of 57 out-patients for minor surgery; 29 were induced with Althesin and 28 with methohexitone, the anaesthetic being supplemented in both groups with an equal proportion of nitrous oxide and oxygen. It was found that, in the circumstances of the trial, the rate of recovery after Althesin compared favourably with recovery after methohexitone, and that Althesin was a suitable drug for out-patient anaesthesia.

The majority of patients were to undergo orthopaedic manipulation and others, removal of the toe nails, cautery of warts or incision of small abscesses. The patients were not premedicated and the duration of surgery in the two groups was 2·2 minutes (mean).

Both intravenous agents were injected as a single dose over about 30 seconds. The dose of methohexitone was 1·2 mg/kg and that of Althesin 0·05 ml/kg.

A control reading had been taken with the ocular test before induction of anaesthesia. Post-operative measurements were made at 10 to 30 minutes after the commencement of the injection. Ten minutes was chosen because, (a) only at about that time could the patients give a reliable reading with the ocular test and, (b) an earlier study had shown that this was a good time to assess the early post-operative defect in

muscle tone. The second reading was taken at a time when recovery should be nearly complete following an anaesthetic suitable for out-patients.

The duration of anaesthesia, as measured from the commencement of injection to the first opening of the eyes on command, was significantly longer in the Althesin group, with a mean of 4·8 minutes (SD $\pm$ 0·9 min), than in the methohexitone group, with a mean of 3·1 minutes (SD $\pm$ 0·3 min).

The ocular divergence 10 minutes after the commencement of injection was on the whole significantly greater in the Althesin group than in the methohexitone group. The difference could be due to the fact that the interval between arousal and test was not the same in the two groups - Althesin five minutes, methohexitone seven minutes. Moreover, the greater ocular divergence in the early post-operative period may partly be due to an apparently greater muscle-relaxant effect of Althesin. 'Such an effect could be of considerable advantage in procedures which particularly require muscle relaxation.'

At 30 minutes after the initial injection, there was no significant difference between the readings in the two groups. However, 13 of the 29 patients in the Althesin group and 11 of the 28 patients in the methohexitone group still showed minor degrees of ocular imbalance. Some of these patients were followed up and in neither group was complete recovery delayed beyond 90 minutes. No complications such as nausea and vomiting occurred in either group in the series and recovery was uneventful in all patients.

The author points out that the ocular test is extremely sensitive and a minor abnormality in ocular balance does not mean that the patient is clinically unsafe.

Haemodynamic effects of Althesin in poor-risk patients

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Postgraduate Medical Journal, 1972, June supplement, 133

The haemodynamic effects of induction with Althesin and thiopentone were compared in two groups of 10 poor-risk patients (AMA classification 2 or 3), mostly with fractured femurs.

In the Althesin group the mean age was 71 years and the mean weight 57 kg; in the thiopentone group 74 years and 51 kg. There were six female and four male patients in each group. No premedication was given. In the anaesthetic room a central venous pressure line was inserted into either the right external jugular or the right median cubital vein; baseline measurements were made.

Either Althesin or thiopentone 2·5 per cent was given slowly until the eyelash reflex disappeared. The dosage of Althesin required varied from 38 to 97 µl/kg (mean 54 µl/kg), and that of thiopentone from 1·1 to 10 mg/kg, (mean 4·0 mg/kg).

From the start of injection serial measurements were made of the pulse rate, systolic and diastolic blood pressures and central venous pressure at minute intervals for six minutes, the patient breathing air spontaneously. After six minutes or when the patient showed signs of returning consciousness, a further small dose of anaesthetic, as well as suxamethonium chloride 50 to 75 mg, was given, and the patient intubated. The operation then commenced.

Two minutes from the start of the thiopentone injection there was a highly significant fall in systolic blood pressure - from 147 to 118 mm Hg (mean values). By four and six minutes, the systolic blood pressure was not significantly depressed (129 mm Hg, mean).

Two minutes after Althesin injection there was also a fall in systolic blood pressure (from 141 to 124 mm Hg, mean values), but this was not significant. At four and six minutes this reduction was maintained.

The pulse rate with the thiopentone group showed individual variation and, in the mean values there was no change at two, four and six minutes. With Althesin there was an insignificant rise in pulse rate at two and four minutes; the rate returned to the baseline value at six minutes, except for one hypertensive patient who had a marked slowing (20 per cent) of the pulse rate at two, four and six minutes.

The central venous pressure measurements were difficult to interpret as the response was so variable in both groups.

The rise in heart rate with Althesin, the authors suggest, could be a compensatory mechanism maintaining the cardiac output. Althesin appeared to be in the circumstances of the study quite suitable for use in poor-risk patients, with the exception of patients who are unable to produce an increase in heart rate to maintain cardiac output.

A comparison of the cardiorespiratory effects during induction of anaesthesia of Althesin with thiopentone and methohexitone

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Postgraduate Medical Journal, 1972, June supplement, 66

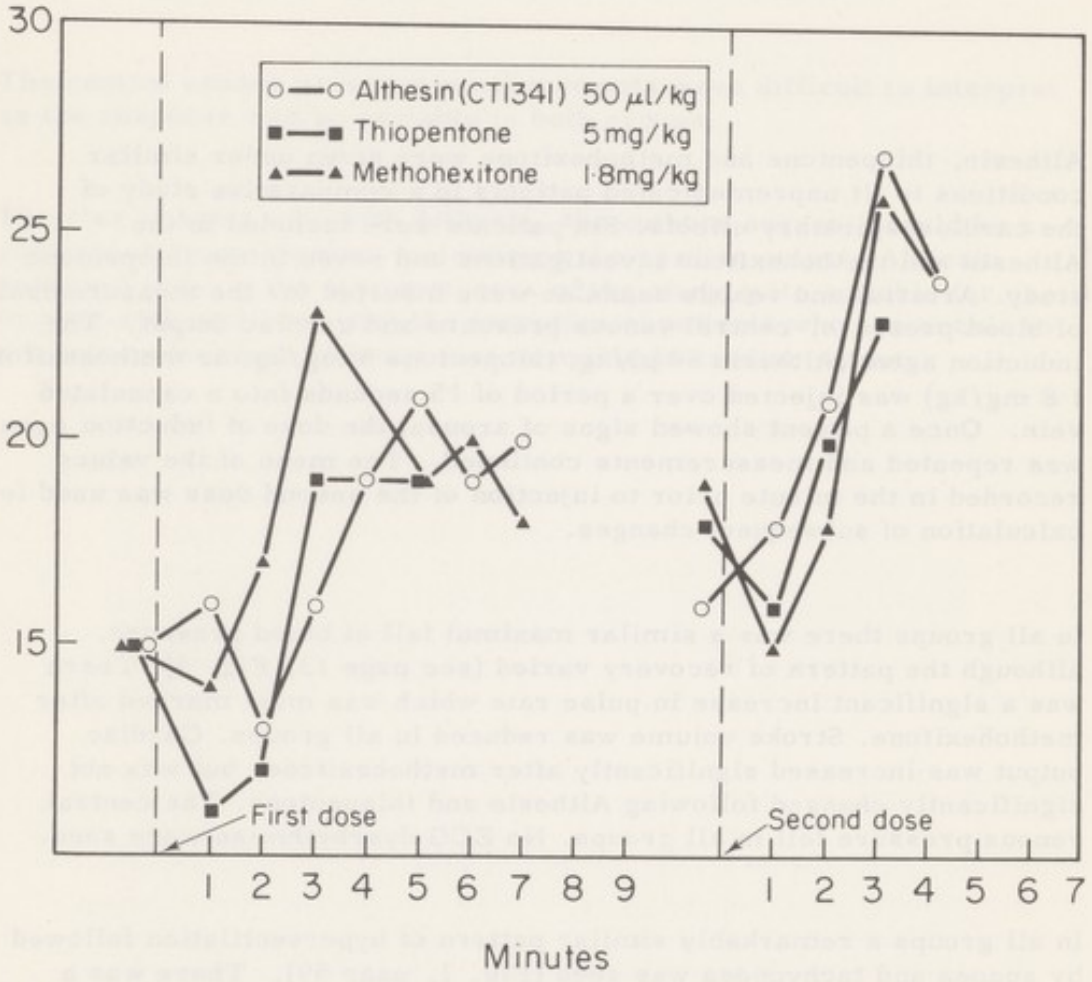
Althesin, thiopentone and methohexitone were given under similar conditions to fit unpremedicated patients in a comparative study of the cardiorespiratory effects. Six patients were included in the Althesin and methohexitone investigations and seven in the thiopentone study. Arterial and venous cannulae were inserted for the measurement of blood pressure, central venous pressure and cardiac output. The induction agent (Althesin 50 µl/kg; thiopentone 5 mg/kg; or methohexitone 1·8 mg/kg) was injected over a period of 15 seconds into a cannulated vein. Once a patient showed signs of arousal the dose of induction agent was repeated and measurements continued. The mean of the values recorded in the minute prior to injection of the second dose was used for calculation of subsequent changes.

In all groups there was a similar maximal fall of blood pressure, although the pattern of recovery varied (see page 13, Fig. 5). There was a significant increase in pulse rate which was most marked after methohexitone. Stroke volume was reduced in all groups. Cardiac output was increased significantly after methohexitone, but was not significantly changed following Althesin and thiopentone. The central venous pressure fell in all groups. No ECG dysrhythmias were seen.

In all groups a remarkably similar pattern of hyperventilation followed by apnoea and tachypnoea was seen (Fig. 1, page 59). There was a similar small rise in arterial carbon dioxide tension and a fall in arterial oxygen tension (PaO_2) in all groups. The fall in PaO_2 was most marked after Althesin but was not significantly different from the other two groups.

Figure 1

Changes in respiratory rate following induction of anaesthesia with Althesin, thiopentone and methohexitone and after a second dose given approximately 11 minutes later.



Times of the two doses are represented by the broken lines.

In their conclusion, the authors comment on the fact that 'two such chemically unrelated groups of induction agents should produce these similar cardiorespiratory changes'.

Studies with Althesin - a new steroid anaesthetic

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Postgraduate Medical Journal, 1972, June supplement, 105

Althesin was used as the sole anaesthetic in dosages of 40, 60, 80 and 100 µl/kg for various minor operations and procedures, in 150 unpremedicated patients. The dose of Althesin administered was related essentially to the expected duration of surgery, but in patients over 60 years the smaller dosages were selected. Forty to 60 seconds after starting the injection the patient had fallen asleep, and surgery commenced. Hypnosis was always satisfactory, but in some cases there was inadequate muscular relaxation for manipulation, especially when a small dose of Althesin had been administered or when muscular contractions occurred. In 109 of the 150 cases there was no visible reflex response to the procedure, which was completed without incident. In 29 cases there was some reflex movement in response to stimulation. In 12 cases anaesthesia was frankly unsatisfactory and there was considerable movement and resistance, although it was possible to complete the procedure without supplementary anaesthesia. Table 1 shows the duration of 'analgesia' in those patients in whom it could be assessed.

Table 1

Time from beginning of injection of Althesin to end of 'analgesia'.

Dosage (µl/kg)	Number of patients	Time (minutes)	Mean (minutes)
60	8	1·25 to 4	2·4
80	8	2·75 to 8·5	5·0
100	11	1·5 to 13	4·6

Following completion of surgery the stages of recovery of consciousness were recorded in 90 patients, aged 16 to 59 years (Table 2).

Table 2

Time from start of injection of Althesin ('0') to three stages of recovery in the patients who received 60, 80 or 100 µl/kg.

Dosage (µl/kg)	Number of patients	Time in minutes from '0' to: eyes open	orientated	sitting up
60	27	6·4 ± 0·51	9·2 ± 0·44	10·5 ± 0·55
80	30	8·4 ± 0·53	12·7 ± 0·52	14·2 ± 0·92
100	27	10·0 ± 0·66	15·4 ± 1·21	15·7 ± 1·05

The duration of action of Althesin was the same in males and females; however, the time taken from the start of injection to each of the stages of recovery was longer in patients over 40 years of age than in those under 40.

The author concludes: 'Althesin is a satisfactory and safe intravenous anaesthetic agent for use in out-patient and minor surgery and gives reasonably rapid recovery.'

Wave analysis of EEG patterns during anaesthesia produced by Althesin

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Postgraduate Medical Journal, 1972, June supplement, 96

In a two-part study it was shown firstly that, the EEG changes produced by Althesin are not restricted to one area of the cortex; and that, after a single dose, the depth of anaesthesia seems to be characterised by an increased proportion of slow-wave activity. The observations were made on eight volunteers.

In the second part of the study, the use of Althesin as the sole anaesthetic agent for upper abdominal surgery was explored. Althesin 0·075 to 0·10 ml/kg body weight was given as the induction dose to 12 patients and this was repeated at 15 to 20 minute intervals. Muscle relaxation was achieved with dextro-tubocurarine and respiration maintained manually. Central venous pressure and arterial pressure were monitored continuously. Blood gases were estimated at frequent intervals so that PaO_2 could be kept above 90 mm Hg by adding oxygen to the inspired air. The duration of anaesthesia varied from 1 hour 48 minutes to 5 hours 52 minutes and the total dose of Althesin from 21·2 ml to 104 ml. The dosage expressed as ml/kg/hour ranged from 0·154 to 0·309.

The greatest increase in heart rate occurred after the first injection; with subsequent injections there was less tachycardia. Blood pressure was seen to be affected by a number of factors. (a) Size of induction dose, the smaller dose caused a fall of approximately 20 mm Hg; the larger dose about 30 mm Hg. (b) The number in sequence of the injections - for example, the average fall during the eighth and ninth administrations was about 6 mm Hg for the 0·075 ml/kg dose and 18 for the 0·10 ml/kg dose. (c) Speed of injection - rapid injection provoked hypotension. (d) Surgical stimulation decreased the hypotension. During recovery painful or vocal stimuli also diminished the fall in blood pressure.

Recovery was prolonged as the number of repeat doses increased. Single doses produced rapid and clear-headed recoveries, as seen in

the EEG study, but patients anaesthetised for a long time were still drowsy when able to respond to verbal command. Once this stage was reached, however, recovery was considerably faster than when thiobarbiturates are used. It was found that Althesin patients complained of pain earlier during recovery than patients given thiamylal or halothane anaesthetics, possibly because they were more awake after Althesin.

Liver function tests, blood cell counts and routine clinical examination showed no change attributable to Althesin during a 10 day follow-up.

Althesin, when used with muscle relaxants, produced satisfactory anaesthesia for upper abdominal surgery in the 12 patients. The study showed that a wide range of dosage can be used safely. Further work is required to investigate the impression that the proportion of slow waves in the EEG can be used to indicate the depth of Althesin anaesthesia.

The respiratory effects of Althesin

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Postgraduate Medical Journal, 1972, June supplement, 85

Study of spirometry changes formed part of the investigation into the respiratory effects of Althesin. Typically after the injection of 8 ml of Althesin over one minute the patient, even before the onset of sleep, began to expire a greater volume than was inspired. The lung volume was decreased by about one litre. After a short period of apnoea, ventilation returned, although slightly depressed, but over the next three minutes there was a rapid return towards the control volume and about half a litre of lung volume was restored. Thereafter the patient returned to the normal oxygen consumption (see Fig. 7, page 15). Such changes were seen in 20 of the 30 patients studied. The ten patients who did not show the decrease in lung volume immediately, were those who developed respiratory obstruction. After a period of apnoea, which varied from a few seconds to almost two minutes, considerable respiratory effort developed but there was no movement of the spirometer pen for a further one minute. The source of the respiratory obstruction seemed to be relaxation of the tongue muscles because obstruction was always relieved by putting in an airway.

In a second part of the trial the effects on lung compliance were studied in ten patients. After injection of Althesin respiration was controlled by using either nitrous oxide/halothane mixtures plus oxygen, or nitrous oxide/curare anaesthesia plus oxygen, with a pre-set volume ventilator. Airway pressure and inspiratory inflow volume were measured. The volume was plotted against the pressure to give pressure volume loops. No change in lung airway resistance or compliance was detected one minute after the administration of Althesin.

Subsequently, to investigate possible sensitisation of the respiratory endothelium to irritant vapours or stimuli, patients were challenged throughout a few breaths with a sudden blast of either 4 per cent halothane or the maximum trichlorethylene concentration obtainable

from a Boyle's bottle. The challenge produced a slight cough in one bronchitic patient whilst actually inhaling the halothane and, within two breaths of discontinuing the halothane, he reverted to normal respiration. The author concludes that Althesin, unlike barbiturates, does not sensitise the respiratory endothelium to the irritant effects of dry gases or vapours.

Laryngoscopy one minute after giving Althesin produced minimal disturbance of respiration; tracheal aspiration could be done very easily under the influence of this drug, with a return to the normal respiratory pattern immediately after withdrawal of the tracheal suction catheter.

Althesin in the dental chair

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Eastman Dental Hospital, London
Postgraduate Medical Journal, 1972, June supplement, 130

Unpremedicated patients were given Althesin, while seated in a dental chair, for single or multiple dental extractions. The series comprised 100 out-patients, 48 men and 52 women, aged between 14 and 65 years; each patient received a dose of 0·05 ml/kg injected over 10 to 15 seconds (except for four cases, given 0·04 ml/kg). Thirty-four patients had Althesin only; 46 were given nitrous oxide/oxygen mixture after induction with Althesin and 20 cases required halothane in addition. The dental procedure lasted under three minutes in 85 patients, and three to six minutes in the remaining 15.

Induction was smooth, pain free and took one arm-brain circulation time. Operating conditions were 'very satisfactory' (no movements present) in 71 cases; 'satisfactory' in 23 cases, and 'poor' (considerable movement making extraction difficult) in six patients - of whom four had received Althesin 0·04 ml/kg, a dose subsequently abandoned. After induction there was sufficient relaxation to introduce a prop and move it from one side of the mouth to the other. Pupillary dilation was common. The blood pressure changes are shown in Table 1.

Table 1

Blood pressure changes following Althesin, before surgery.

Blood pressure change	Number of patients
Rise of 11 to 20 mm Hg	6
Remained the same or within ± 10 mm Hg	56
Fall of 11 to 20 mm Hg	32
Fall of 21 to 40 mm Hg	6

During the operative procedure there was some hypertensive effect - presumably a response to surgical stimulation. The average rise in pulse rate was 17·6 beats/min. Both blood pressure and pulse rate returned to normal in the recovery room. ECG lead 1 monitoring in 30 patients showed no arrhythmias. A few patients had transient apnoea following induction but, overall, the respiration rate rose an average of 1·9 breaths per minute.

The side effects consisted of muscle movement (including any response to surgical stimuli) in 30 cases, tremors of upper or lower limbs or spasm of the arms in 15 cases, and cough and spasm in 8 cases. No true case of laryngospasm was seen during induction. The coughing may have been due to inadequate packing permitting blood to trickle into the pharynx. There were no instances of hiccoughs or salivation. There was a 'marked absence' of post-operative nausea and vomiting, or headache. No local effects were seen. The time to recovery is shown in Table 2.

Table 2

Time from injection of Althesin to various stages of recovery.

Stages of recovery	Average time (minutes)	Range (minutes)
Response to 'open your eyes'	3·33	1·25 to 6·15
Leaving dental chair	5·24	3·0 to 9·48
Full orientation	6·06	4·0 to 8·45
Rhomberg negative	13·99	6·0 to 34·45

Crying and apparent distress occurred in 33 patients during the recovery period in the dental chair. When muscle tone and protective reflexes returned, there was a very marked disinclination to move and, unless vocally encouraged to open their eyes, patients continued to sit in a dazed state. Active assistance was needed in all cases when leaving the dental chair. The author found that 'the apparent distress of 33 per cent of patients at recovery is perversely contradicted by a patient acceptance of 100 per cent, expressions of "fabulous", "fantastic", "nice" and "good" being common. Amnesia for the procedure has been total'.

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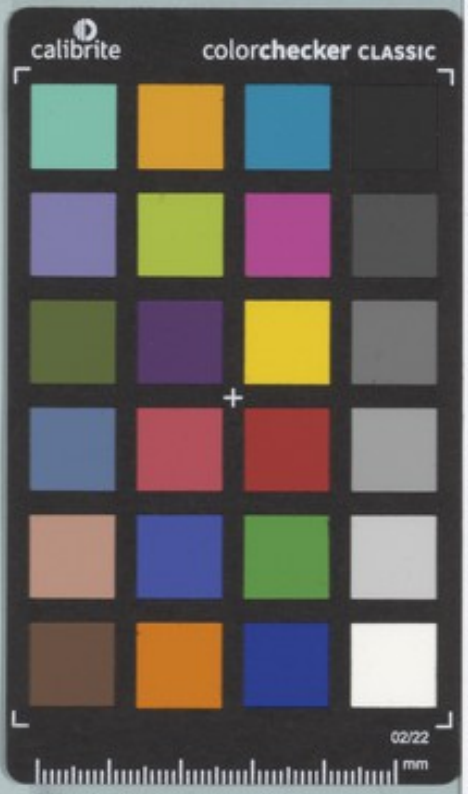
ALTHESIN

(CT1341)

Intravenous anaes

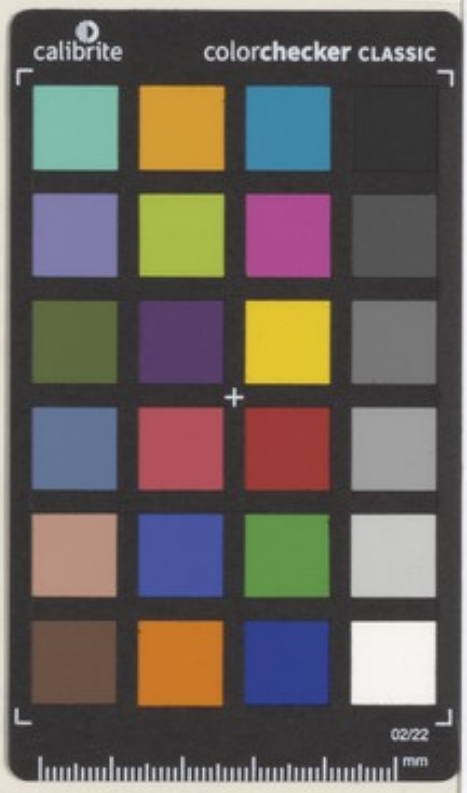
Glaxo



ALTHESIN

(CT 1341)

Intravenous anaesthetic



Althesin is a Glaxo trade

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