3 patients over 48 hours reached 70–80%. High-voltage electrophoresis and radioassay of urine samples taken at 80 minutes and 4 hours after administration of $^{3}H$ AH8165 showed that the radioactivity was excreted as unchanged $^{3}H$ AH8165. The loss of tritium to $^{3}H_2O$ was less than 1%. Possibly in man the remaining radioactivity was excreted in the bile.

**Dr R S J Clarke, Professor J W Dundee and Dr I W Carson**
*(Department of Anæsthetics, The Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast, BT12 6BJ)*

**A New Steroid Anæsthetic – Althesin**

The anæsthetic properties of steroids have been known since Hans Selye in 1942 published his results of screening 75 different steroids. The most promising compound identified at this stage was pregnanedione. Experimentation continued slowly and in 1955 P'An *et al.* reported their findings with hydroxydione a substance closely related to pregnanedione but with the long sodium succinate group attached to the $^{21}C$ atom. It had two main drawbacks: the slow onset of anæsthesia, and the production of venous thrombosis; and three advantages: water solubility, a wide safety margin due to lack of medullary depression, and postoperative euphoria and lack of sickness.

Further research was concentrated on production of a steroid which was also water-soluble but with a rapid onset of action and without the irritant properties; so far no such substance has been found. However, 2 steroids (known as alphaxalone and alphadolone acetate) have been combined in the anæsthetic Althesin which has many advantages over the earlier steroid (Child *et al.* 1971). Both are anæsthetic agents, alphaxalone being the more potent; in fact, alphadolone acetate was only added to increase the solubility of the principal substance. Though they are not soluble in water they can be made soluble by the addition of Cremophor EL, a polyoxyethylated form of castor oil.

Cremophor EL is the solubilizing agent of propanidid and, although it would be preferable to use water-soluble anæsthetics, it should be emphasized that there is no evidence of any toxic action from Cremophor in man. It liberates histamine to a dangerous extent in the dog but not in man, as was conclusively shown by Lorenz *et al.* (1972). Administration of Cremophor EL in the doses used in Althesin has no significant effect on blood pressure, heart rate or central venous pressure (Savege *et al.* 1971). It seems likely, therefore, that the known toxic effects of propanidid and the various minor reactions to Althesin are due to the drugs themselves and not to the solvent.

The early pharmacological studies of Glaxo Research Laboratories (Child *et al.* 1971) demonstrated that Althesin was rapid-acting with a high therapeutic index. In addition it was non-irritant to animals when injected intravenously or intra-arterially. The main experimental work is now concentrated on establishing the distribution and fate of the steroids and autoradiography has shown that they or their metabolites are selectively concentrated in the liver and kidney. Further work showed that an important link in the excretory pathway was the enzyme glucuronyl transferase, since animals deficient in this enzyme slept for an abnormally long time after a single dose of Althesin (Child *et al.* 1972). In spite of these pointers the subject of metabolism still needs exploring, particularly the question of enterohepatic circulation.

This paper reviews the actions of Althesin in man from the following points of view: (1) How does it compare with the standard induction agents? (2) Does it have any of the disadvantages of hydroxydione? (3) Has it any advantages over the standard drugs which justify its introduction into clinical practice?

The most obvious disadvantages of methohexitone and propanidid are the involuntary muscle movements and hiccup which occur after induction. The incidence of the muscle movements after standard equipotent doses and atropine premedication is 33% with methohexitone, 18% with Althesin, 11% with propanidid, and 9% with thiopentone. Hiccup is rare after all these drugs except methohexitone (Clarke *et al.* 1971). As with other intravenous anæsthetics, these side-effects are dose related, but the percentage of unsatisfactory induction only becomes a problem above the 100 $\mu$l/kg dose range of Althesin.

The cardiovascular side-effects follow a similar pattern but the incidence of hypotension of more than 20 mmHg appears to be very similar with all standard agents (10–15%) in patients of

ASA physical status grades 1 and 2. The high therapeutic index in mice suggested there might be less cardiac depression with this drug but despite intensive study there appears to be little essential difference between various induction agents. Savege *et al.* (1971) found that there were similar falls in blood pressure, central venous pressure and stroke volume during induction with Althesin, methohexitone and thiopentone. The heart rate rose significantly with the three agents so that the cardiac output was not significantly altered.

Lyons & Clarke (1972), in a group of heavily premedicated patients awaiting cardiac surgery, also found a significant and similar fall in blood pressure with the same agents. In this study the heart rate after Althesin did not rise significantly. A third study by Prys-Roberts *et al.* (1972) in hypertensive patients also revealed a significant fall in arterial blood pressure, rise in heart rate and fall in stroke volume with maintenance of the cardiac output. These changes are very similar to findings by this group with other intravenous anæsthetics.

Recovery after Althesin appeared, at first, to be more rapid than after thiopentone or methohexitone but less so than after propanidid (Clarke *et al.* 1971). However, this is not a unanimous finding (*see* Foley *et al.* 1972, Hannington-Kiff 1972). A detailed study is now being carried out of recovery after different doses of Althesin and other intravenous anæsthetics. The times from induction to a number of clearly defined end-points (first response to commands, ability to perform skilled tasks, &c.) have been noted and the findings after thiopentone and Althesin are seen in Fig 1. The skilled task studied was the transference of 6 little pegs from one perforated area to another at a speed comparable to that before anæsthesia.

Fig 1 shows the waking time and the time of return of skilled movement as described. Equipotent low doses of thiopentone 4 mg/kg or Althesin 50 $\mu$l/kg were followed by equally rapid recovery of consciousness and skilled movement. On the other hand, when the doses of both were doubled to Althesin 100 $\mu$l/kg against thiopentone 8 mg/kg, the latter led to much more prolonged drowsiness.

The duration of action can also be studied by keeping patients anæsthetized for an hour or more with only the intravenous agent and nitrous oxide. Equipotent induction doses of thiopentone, methohexitone and Althesin were followed by further increments of the agent when the patient required them. When the cumulative dosage is plotted against time, there is a high requirement after propanidid indicating a short duration of action and little cumulation. Althesin has a longer duration of action and thiopentone longer still but, in addition, the curve for thiopentone flattens out suggesting progressive accumulation of the drug in the body as distinct from rapid breakdown of the other drugs.

As well as allowing rapid recovery, Althesin anæsthesia is followed by less sickness than other intravenous anæsthetics (Clarke *et al.* 1971)

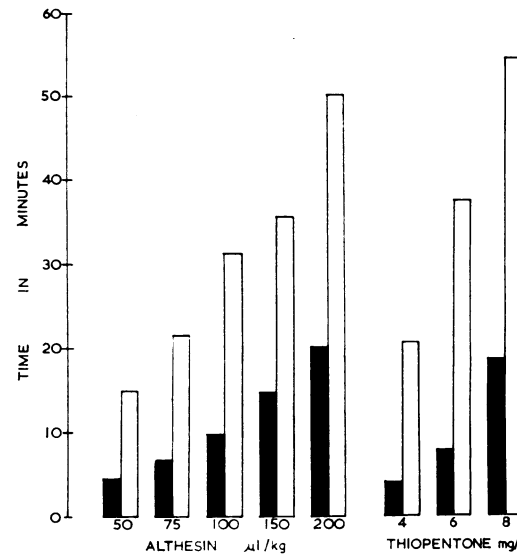


Fig 1 *Recovery times of groups of 10 patients having various doses of Althesin or thiopentone. The dark columns represent time to first opening of the eyes, the clear columns the time until patient was able to perform a skilled task at normal speed* (see text)

Hydroxydione has clearly a slow onset of action but it is difficult to make a controlled study of the speed of onset with an intravenous drug because of the wide variation in arm-brain circulation times. However, some standardization can be achieved by excluding patients with cardiac disability and by injecting during reactive hyperæmia so that the arm-brain circulation is accelerated. A range of doses (20–100 $\mu$l/kg) has been given under these conditions and the onset of sleep timed from end of injection until patients were unable to count aloud (Clarke *et al.* 1972). When the points from Althesin were plotted on a scale of equipotency with methohexitone and thiopentone, they fell broadly along the same line, indicating that the onset of sleep with the 3 drugs is very similar.

The irritant properties of hydroxydione were the main factor leading to its withdrawal from clinical use. Over the intervening years controlled studies were made to compare the barbiturates with propanidid and now with Althesin. In all cases a predetermined dose of the drug was given, the needle removed from the vein immediately and the site pressed for 1–2 minutes. The vein used was noted and was examined by the anæsthetist 1, 2 and 3 days later for redness, thrombosis, and thrombosis plus pain (Carson *et al.* 1972). The incidence of complications was significantly lower with Althesin than with 5% thiopentone, though similar to the incidence with the 2½% solution or with 1% methohexitone. Clearly the change from the water-soluble hydroxydione to the almost insoluble steroids of Althesin has been an improvement, and venous damage following propanidid cannot be attributed to the Cremophor EL.

We have found (unpublished) no rise in plasma cortisol or blood sugar following the use of Althesin during minor surgery. Extensive liver function tests have shown no effects attributable to the drug except in 1 patient with carcinoma of the breast who had a transitory large increase in transaminases. Possible potentiation of the action of suxamethonium has also been looked for in view of the interaction between propanidid and this relaxant. However, in this respect the steroid behaves very similarly to the barbiturates (Carson *et al.* 1973).

Regarding the possible place of Althesin in anæsthetic practice, two groups of 10 patients each have been anæsthetized for Cæsarean section with intermittent doses of Althesin or thiopentone. The babies were delivered between 5 and 20 minutes later and were assessed on the standard Apgar scoring with blood gases in addition. At 1 and 5 minutes after delivery the babies in the Althesin series were in better condition than those having had thiopentone, but the difference had passed when observations were made at 10 minutes. Autoradiographic studies have shown Althesin in the fetal liver of the rat within 3 minutes of injection so that lack of anæsthesia in the newborn is not due to failure of Althesin to cross the placental barrier (Child *et al.* 1972). The most likely explanation is that metabolism of Althesin in both mother and baby was more rapid than that of thiopentone.

Clearly Althesin will be accepted or rejected by the opinion of the majority of clinical anæsthetists, and to assess this a group trial has recently been carried out in Belfast. Seventy anæsthetists were each asked to use Althesin for 40 inductions in their standard practice, and the results of these have been analysed in detail. Altogether, 95% of patients had almost trouble-free inductions and only 0.5% had serious problems. Involuntary muscle movements and hypertonus formed the majority of complaints, but the incidence was clinically acceptable. Inadequate depth of anæsthesia following the recommended dose of 50 μl/kg was common and probably 60–75 μl/kg is more satisfactory in most anæsthetists' routine practice.

The role of Althesin is obviously not yet defined but it could perhaps be summarized by saying that: (1) it is stable in solution and only 3–5 ml of the current solution is required; (2) it is of shorter duration of action than thiopentone when used for minor surgery and rapid clear-headed recovery can be achieved; and (3) it has a high safety margin.

REFERENCES

Carson I W, Alexander J P, Hewitt J C & Dundee J W (1972) *British Journal of Anæsthesia* 44, 1311–1313
Carson I W, Clarke R S J & Dundee J W (1973) *British Journal of Pharmacology* 47, 679P
Child K J, Currie J P, Davis B, Dodds M G, Pearce D R & Twissell D J (1971) *British Journal of Anæsthesia* 43, 2–13
Child K J, Gibson W, Harnby G & Hart J W (1972) *Postgraduate Medical Journal* 48, Suppl. 2, pp 37–43
Clarke R S J, Dundee J W & Carson I W (1972) *Postgraduate Medical Journal* 48, Suppl. 2, pp 62–65
Clarke R S J, Montgomery S J, Dundee J W & Bovill J G (1971) *British Journal of Anæsthesia* 43, 947–952
Foley E I, Walton B, Savege T M, Strunin L & Simpson B R (1972) *Postgraduate Medical Journal* 48, Suppl. 2, pp 112–115
Hannington-Kiff J G (1972) *Postgraduate Medical Journal* 48, Suppl. 2, pp 116–119
Lorenz W, Doenicke A, Meyer R, Reimann J, Kusche J, Barth H, Geesing H, Hutzel M & Weissenbacher B (1972) *British Journal of Anæsthesia* 44, 355–369
Lyons S M & Clarke R S J (1972) *British Journal of Anæsthesia* 42, 575–583
P'An S Y, Gardocki J E, Hutcheon D E, Rudel H, Kodet M J & Laubach G D (1955) *Journal of Pharmacology and Experimental Therapeutics* 115, 432–441
Prys-Roberts C, Foex P & Biro G P (1972) *Postgraduate Medical Journal* 48, Suppl. 2, pp 80–84
Savege T M, Foley E I, Coultas R J, Walton B, Strunin L, Simpson B R & Scott D F (1971) *Anæsthesia* 26, 402–413
Selye H (1942) *Anæsthesia and Analgesia. Current Researches* 21, 41–47

**Dr T M Savege** (*The London Hospital, London E1*), discussed two areas where Althesin might prove particularly useful: as part of pollution-free anæsthesia, and for sedation. Pollution of the environment with volatile vapours and anæsthetic gases might be detrimental to health (Askrog & Harvald 1970, Cohen *et al.* 1971, Whitcher *et al.* 1971), and it was unlikely that the venting of such drugs into the theatre atmosphere would be permitted in the future. Members of the Anæsthetic Department of The London

*Table 1*

**Levels of sedation**

| | |
|---|---|
| (1) Agitated and/or anxious<br>(2) Cooperative and calm<br>(3) Responsive to commands only | Awake |
| (4) Rousable<br>(5) Unrousable | Asleep |

Hospital had been trying to perfect a pollution-free anæsthetic technique. A continuous infusion of Althesin (20 ml diluted into 250 ml 5% dextrose) was given *via* a pædiatric giving-set and a butterfly needle placed in the back of the hand. The infusion rate was modified to keep the patient asleep. Increments of an analgesic drug were necessary and might be given through a three-way tap in the infusion line. The patient breathed a mixture of air and oxygen to give a 30% inspired oxygen concentration. To date over 120 patients, aged 3–85 years, had been anæsthetized with this technique; 25 had also been paralysed, intubated and ventilated. The mean duration of surgery was 33 minutes and the mean dose of undiluted Althesin required was 15.9 ml (s.d. $\pm$10.1). Although the technique took some time to master, the quality of anæsthesia was assessed as good or excellent in over 90% of cases. Possibly, therefore, this type of pollution-free anæsthesia would replace some of the present conventional methods.

The second possible use of Althesin was for sedation. Presently available sedatives did not allow precise control of sedation. Agents such as diazepam might fail to be effective until large doses were given; this could result in prolonged heavy sedation which in some instances was undesirable. For example, patients with combined head and chest injuries might require sedation for management of the crushed chest that interfered with the continuous assessment of the cerebral state. It would be a great advantage to be able to sedate patients to the required degree and yet guarantee that the effects would wear off rapidly if the drug were discontinued. At the London Hospital Althesin 5 ml added to 25 ml 5% dextrose had been used as a continuous intravenous infusion for this purpose, using a pædiatric burette and an IVAC 501 infusion pump. The desired level of sedation (Table 1) was selected by the physician, and the nurse maintained that level by controlling the drip rate. To date over 20 patients with a variety of conditions such as respiratory failure, head injury, myasthenia gravis, and following heart surgery, had been sedated for periods from 1 hour to over 10 days. The dose of undiluted Althesin ranged from 3 to 1930 ml.

Both the quality of sedation and its control had been good and no serious adverse effects had been encountered. Once the infusion was discontinued the effect of Althesin rapidly wore off, the patient becoming fully cooperative within 10–15 minutes. Although further experience was necessary it looked as though Althesin would provide precisely controlled sedation, something that had not been possible before.

REFERENCES

**Askrog V F & Harvald B**
(1970) *Nordisk Medicin* **83**, 498
**Cohen E N, Bellville J W & Brown B W**
(1971) *Anesthesiology* **35**, 343
**Whitcher C E, Cohen E N & Trudell J R**
(1971) *Anesthesiology* **35**, 348