# Section of Anæsthetics

*President* A I Parry Brown FFA RCS

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# New Drugs in Anæsthesia

**Dr C E Blogg, Dr T M Savege, Dr J C Simpson, Miss L A Ross and Professor B R Simpson**
*(Anæsthetics Unit, The London Hospital, Whitechapel, London E1*

## A New Muscle Relaxant – AH8165

Currently available muscle relaxants have many disadvantages. The slow onset of action of nondepolarizing drugs may be dangerous if the patient has a full stomach, and their prolonged action may imperil the safety of the patient in the postoperative period.

Of the depolarizing muscle relaxants, suxmethonium has a number of undesirable features, but its rapid speed of onset permits swift intubation in the unprepared patient. Nevertheless, muscle fasciculations may cause a rise in the intragastric pressure (Miller & Way 1971) predisposing to regurgitation of gastric contents.

The qualities essential to an ideal muscle relaxant would be: nondepolarizing action; rapid speed of onset; short duration; either rapid excretion of the unchanged drug or rapid metabolism and pharmacologically inactive metabolites; clean reversibility with anticholinesterases; specific action upon the neuromuscular junction; no clinically significant placental or blood-brain transfer; and no local or systemic side-effects.

A drug with a short duration of action would be valuable both for short periods of relaxation and, by varying the rate of administration of the drug, for longer operations without residual effects. AH8165 is the most potent of a group of tetrazine-dyes with nondepolarizing relaxant action. Results from work in small animals (Bolger *et al.* 1972; Brittain & Tyers 1972, 1973) indicated that AH8165 possesses many of the properties of the ideal muscle relaxant.

The initial investigation of the action of AH8165 in man (Simpson *et al.* 1972) using a modified isolated limb technique (Feldman & Tyrrell 1970) indicated that AH8165 has a rapid onset of action, but unfortunately the duration of action was longer than in small animals.

Subsequently the actions of AH8165 were investigated in patients, all of whom had given informed consent, and its characteristics compared with some of the listed properties of the ideal muscle relaxant.

*Nondepolarizing Muscle Relaxant Properties*
The properties characteristic of a nondepolarizing muscle relaxant (Wylie & Churchill-Davidson 1972, Feldman & Tyrrell 1969) were demonstrated since no muscle fasciculations were seen, the twitch height of the adductor pollicis contraction decreased rapidly, fade occurred with stimulation of the ulnar nerve at both slow and fast rates, and persistent post-tetanic facilitation was demonstrated. The neuromuscular block was readily reversible with neostigmine.

*Speed of Onset*
Variations in circulation time between patients affect the speed of onset of action of muscle relaxants (Harrison & Junius 1972). The speed of onset, shown by first depression of twitch response to 0.5 Hz, of AH8165 given by a central venous catheter increased with increasing dose and compared favourably with the speed of onset following suxamethonium 50 mg given to similar patients (Table 1).

*Table 1*

**Comparison of speeds of onset of AH8165 with suxamethonium shown by twitch response to 0.5 Hz stimulus. (Drugs administered through a central venous catheter)**

| *Drug* | *No. of patients* | *First depression (seconds)* | *Maximum depression (seconds)* | *Depression of response (percentage)* |
|---|---|---|---|---|
| AH8165 0.25 mg/kg | 8 | 32.0 (±9.5) | 151.0 (±99.4) | 82 |
| AH8165 0.5 mg/kg | 3 | 16.5 (±3.5) | 37.0 (±8.3) | 100 |
| AH8165 1.25 mg/kg | 3 | 18.0 (±2.0) | 31.0 (±2.5) | 100 |
| Suxamethonium 50 mg | 4 | 26.0 (±9.4) | 59.5 (±17.0) | 100 |

When AH8165 was given into a peripheral vein, the speed of onset of first depression and maximum depression of twitch height broadly increased with increasing dose until a dose of approximately 0.75 mg/kg was given (Table 2).

*Table 2*

**Comparison of speeds of onset of different doses of AH8165 shown by twitch response to 2 Hz stimulus. (Drugs administered into a peripheral vein)**

| *Dose of AH8165* | *First depression (seconds)* | *100% depression (seconds)* |
|---|---|---|
| 0.5 mg/kg | 30 (18–48) (4 patients) | 73 (46–78) (4 patients) |
| 0.75 mg/kg | 24 (12–36 (9 patients) | 39 (19–48) (10 patients) |
| 1.0 mg/kg | 23 (18–27) (3 patients) | 45 (36–55) (3 patients) |

The times to apnœa in two small series of patients demonstrated that the time to onset of apnœa following peripheral administration of AH8165 is comparable with the times observed following suxamethonium.

*Intubating dose:* The dose of AH8165 necessary for easy endotracheal intubation ranges from 0.5 to 1.25 mg/kg; in the majority of patients 0.75 mg/kg is adequate for easy intubation. However, it is well known that the response to muscle relaxants varies widely between patients (Katz 1967, Miller *et al.* 1972); AH8165 is no exception with an effective range of 0.5–1.25 mg/kg.

*Duration of Action*

The duration of action of muscle relaxants also varies widely (McIntyre & Gain 1971). It is not yet possible to give a precise figure for the duration of action of AH8165 (Table 3) but it is broadly dose-related. Our clinical impression is that the duration of action of AH8165 is comparable with that of gallamine but marginally shorter than that of pancuronium. Coleman *et al.* (1973) recommended an upper dose level of 100 mg for fear of producing an unduly prolonged effect. In our experience so far the largest dose given totalled 255 mg over a 6-hour period. No undue prolongation of effect was found in this or other patients given more than 100 mg AH8165.

*Reversibility*

The reversibility of AH8165 was compared with that of *d*-tubocurarine. Anæsthesia was induced with thiopentone 5.5 mg/kg and phenoperidine 1.0 mg or fentanyl 0.1 mg. After endotracheal intubation intermittent positive pressure ventilation (IPPV) was continued, maintaining end tidal $CO_2$ at 4–5%. Incremental doses of AH8165 or *d*-tubocurarine were given until the twitch height had been reduced to some 10% of the control twitch response, then 25% of the total dose of relaxant already given was administered. Five minutes later, neostigmine 0.05 mg/kg with atropine 0.02 mg/kg was given.

Recovery of twitch height after AH8165 was consistently more rapid than that following *d*-tubocurarine under similar conditions. Miller *et al.* (1972) and Monks (1972) have shown that the reversibilities of *d*-tubocurarine and pancuronium are similar and each is more readily reversible than gallamine. By inference, AH8165 is more readily reversible than pancuronium and gallamine.

*Specific Action*

It is desirable that a muscle relaxant should act specifically upon the neuromuscular junction. To investigate the cardiovascular effects of AH8165, an anæsthetic technique was adopted for fit, unpremedicated patients which ensured that halothane was not necessary and that arterial carbon dioxide tension could be maintained constant. Measurements of cardiac output, arterial blood pressure, central venous pressure (CVP), heart rate, and rate and depth of chest movement were made. After at least 5 minutes of cardiovascular stability, anæsthesia was

*Table 3*

**Times to return of twitch response to 2 Hz stimulus after AH8165**

| *Dose of AH8165* | *Time to return of twitch response* |
|---|---|
| 0.5 mg/kg (4 patients) | 25.0 (15–42) min |
| 0.75 mg/kg (10 patients) | 41.7 (21–82.5) min |
| 1.0 mg/kg (3 patients) | 49 (40–61) min |

induced with thiopentone 5 mg/kg, and after intubation following suxamethonium 50 mg, anæsthesia and IPPV were maintained with nitrous oxide, oxygen (6:2) and phenoperidine 30 μg/kg. End tidal carbon dioxide percentage was measured at a point near the carina and was used as an index of stability of $Paco_2$, subsequently confirmed by blood gas analysis. Rapid measurements of cardiac output were made using an indicator (indocyanine green) dye dilution technique and cardiac output computer (Lexington). At least 20 minutes were allowed to elapse to ensure that induction of anæsthesia and institution of IPPV would not affect the changes produced by injection of AH8165.

It had previously been found that, when this technique is imposed on patients, a marked bradycardia, dramatic falls in cardiac output and blood pressure, and an increase in CVP result. If a muscle relaxant drug is administered under these circumstances the subsequent cardiovascular changes may give a misleading impression of the effects of the drug. Incremental doses of intravenous atropine were therefore injected until the heart rate was restored to near or above awake levels.

A further 5-minute period of cardiovascular stability was recorded and then 0.5 mg/kg AH8165 was injected.

The circulatory effects of this dose of AH8165 in these patients were to raise the heart rate and cardiac output and decrease CVP. The mean blood pressure fell transiently (Fig 1). None of these changes was as marked as those reported in patients in whom the heart rate prior to injection of AH8165 had not been restored to awake values (Savege *et al.* 1973; Coleman *et al.* 1973).

*Histamine:* Blood histamine levels were measured by a fluorimetric technique (Martin & Harrison 1973) before administration of AH8165 and at 1, 3, 6 and 20 minute intervals afterwards. Despite wide variations in resting blood histamine levels no increase occurred to account for the cardiovascular changes observed following AH8165 (Table 4).

*Placental Transfer*

Initial work in pregnant rats, rabbits and dogs (Blogg *et al.* 1973) showed that maternal paralysing doses of AH8165 had no effect on fetal motility. AH8165 (0.6–0.75 mg/kg) was given to 2 patients undergoing termination of pregnancy by vacuum aspiration. No AH8165 was detectable in the uterine aspirate using a rat phrenic nerve diaphragm preparation. Subsequently cord blood

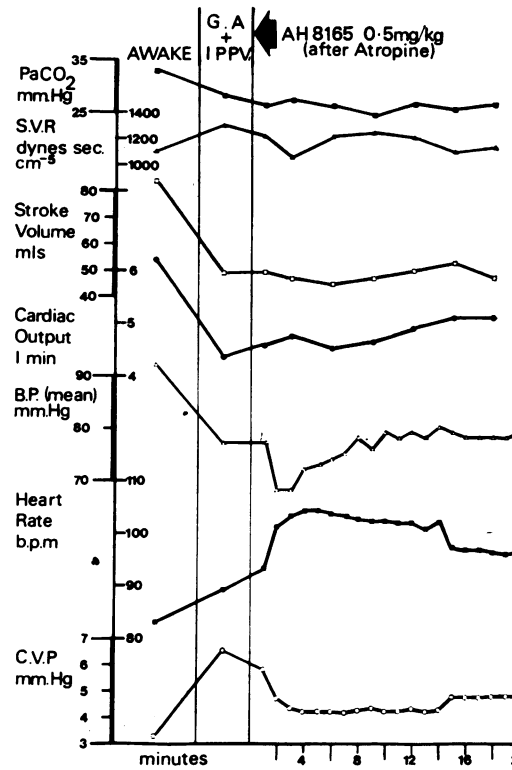


Fig 1 *Cardiovascular effects of AH8165 0.5 mg/kg following incremental doses of atropine. Mean values of 5 patients. SVR, systemic vascular resistance*

samples were taken from the fetuses of 3 patients undergoing termination of pregnancy by hysterotomy, after AH8165 (0.75–1.25 mg/kg). No AH8165 was detectable in 2 of the 3 fetal cord samples, and in the third, AH8165 was present at less than one-tenth of the maternal venous level at the time of delivery.

Finally 6 patients undergoing elective Cæsarean section at or near term, with clinically normal placental function, were given AH8165 0.5–0.95 mg/kg. No AH8165 was detectable in umbilical vein samples. There was no clinical evidence of

*Table 4*

**Effect of AH8165 0·5 mg/kg on blood histamine levels**

| | *Whole blood histamine values (ng/ml)* | | | |
|---|---|---|---|---|
| | | *After AH8165 0.5 mg/kg* | | |
| *Patient* | *Before AH8165* | *1 min* | *6 min* | *20 min* |
| 1 | 15.6 | 19.2 | 15.6 | 13.2 |
| 2 | 40 | 41 | 44 | 45 |
| 3 | 110 | 110 | 108 | 95 |
| 4 | 33 | 48 | 40 | 38 |
| 5 | 69 | 52 | 52 | 51 |

any effect on motility of the infants, but one infant, after a difficult and prolonged delivery, initially breathed and moved normally then required ventilation for 3 minutes. Since recovery was rapid, placental transfer of AH8165 was not thought to be responsible for this problem. It is concluded that AH8165 is not transferred across the placenta in clinically significant amounts.

*Summary*

AH8165 is a nondepolarizing muscle relaxant, with a rapid speed of onset and relatively clean reversal. No local or systemic adverse side-effects have been found. Clinically insignificant placental transfer occurs. On the evidence so far, AH8165 is indicated whenever a nondepolarizing muscle relaxant is required. Because of its rapid speed of onset without a rise in intragastric pressure it is particularly useful when the risk of regurgitation is high. It differs principally from the ideal muscle relaxant in that its duration of action is longer than had been expected.

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**Dr A R Hunter** (*Department of Anæsthetics, Manchester Royal Infirmary*) said that work that was done by Srinivasan *et al.* (1973) in his Department had indicated that in lower animals AH8165 was rapidly metabolized to inactive derivatives. Using the rat phrenic nerve diaphragm preparation as the assay tissue, they had investigated some of the factors modifying the metabolism of AH8165 by rat liver homogenates *in vitro*. The rate of disappearance of AH8165 from the homogenate was markedly enhanced when the liver-donating rats had been starved or pretreated with phenobarbitone or diazepam. In contrast, SKF525A (proadifen hydrochloride) decreased the rate of disappearance of AH8165 from the homogenate. Thus, in the rat, the enzyme responsible for the inactivation of AH8165 was induced and inhibited by the commonly accepted enzyme inducing or inhibiting agents.

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**Dr L E Martin** (*Allen & Hanburys Ltd, Ware, Hertfordshire*) said that *in vitro* under anaerobic conditions AH8165 was reduced to a 3-methyl-2-phenyl-1H-imidazo [1, 2-a] pyridinium salt, methyl imidaze pyridinium (MIP), and under aerobic conditions to MIP plus AH9380 (2-(p-hydroxyphenyl)-3-methyl-1H-imidazo [1, 2-a] pyridinium salt). *In vivo* the metabolism was species-dependent; the rabbit reduced the compound to AH9380 and excreted it as a conjugate in the fæces, whereas the dog and man excreted initially AH8165 unchanged and later a conjugate of AH9380.

**Dr Blogg** said that the metabolism of AH8165 had been studied in man and animals using tritium-labelled AH8165. The conversion of AH8165 in animals to the tertiary amine MIP had been demonstrated under anaerobic conditions using a rat liver homogenate. The MIP molecule could then be further metabolized *in vivo*, first to an hydroxylated form, and then conjugated to glucuronide.

In man, little radioactivity was taken up by red cells. Radioactivity was cleared rapidly from plasma with a plasma half-life of 5–10 minutes. Plasma radioactivity declined so that 96 hours after injection of the drug none was detectable. Most of the radioactivity was excreted in the urine with an initial rapid excretion over the first 4 hours. The cumulative urinary excretion in

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