Clinical Evaluation of a New Non-depolarising Muscle Relaxant

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SUMMARY

Certain pharmacological effects of a new non-depolarising muscle relaxant, AH 8165 (Glaxo), were studied in 50 patients. The adequate dose for muscle relaxation onset of action, duration of effect and reversibility with cholinesterase agents, were established. Changes in blood pressure, heart rate, intra-ocular pressure, blood gases and acid-base values were measured.

In comparison with pancuronium bromide, the onset of action was much more rapid, but the duration of effect was the same. Reversal with anticholinesterase agents was good, and no residual hypoventilation could be detected postoperatively.

S. Afr. Med. J., **48**, 2561 (1974).

The pharmacology of a new non-depolarising neuromuscular blocking agent, 1,1′-azobis(3-methyl-2-phenyl-1 H-imidazo (1,2-*a*)-pyridinium) dibromide (AH 8165) (Fig. 1), has been studied in detail in different animal species.[1] It has been shown to produce a rapid onset of muscular blockade with a short duration of action, comparable to the effects of succinylcholine. Encouraging results have also been obtained in man.[2-4]

Permission was obtained from the Drug Control Council to use AH 8165 (supplied by Glaxo-Allenbury) in a controlled clinical trial.

In this investigation, AH 8165 was administered to 50 patients under general anaesthesia and in whom routine general surgical and thoracic procedures were performed. The purpose of the study was explained to all patients and consent was obtained. The study was conducted in two parts: (*i*) evaluation and (*ii*) clinical comparison with pancuronium bromide.

EVALUATION

The purpose of the first part of the study was to determine an adequate dose for muscle relaxation, the rate of onset of action, the duration of effect and the reversibility with anticholinesterase agents.

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AH 8165

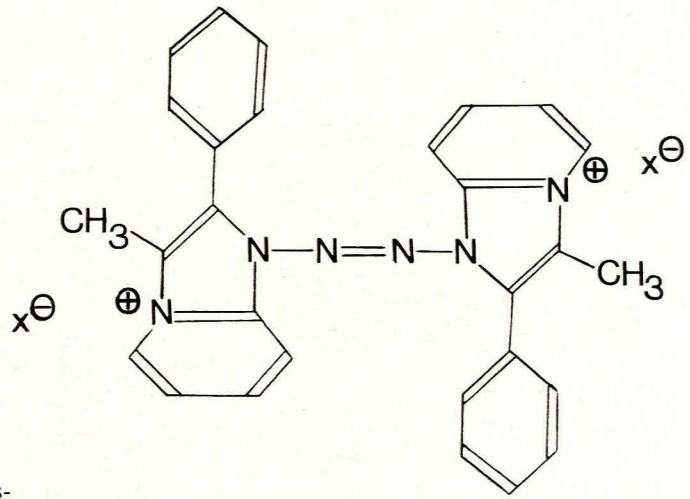

Fig. 1. Chemical structure of AH 8165.

Methods

The drug was administered to 20 patients, who were all premedicated with atropine only. After induction with sodium thiopentone, anaesthesia was deepened with halothane and nitrous oxide, and endotracheal intubation was carried out after topical anaesthesia of the larynx with 4% lignocaine.

The force of the thumb adduction was measured by using a modification of the method described by Tyrrell.[5] A nerve stimulator was used to deliver supramaximal stimuli at a rate of 0,5 Hz to the ulnar nerve at the wrist through 23-gauge needle electrodes inserted subcutaneously. A transducer (Statham UC (3-gold cell)) surmounted by a load cell accessory (UL 4 - 5) to provide a convenient working range (0 - 2,3 kg), was imbedded in a perspex hand grip, with a perspex cradle accommodating the thumb. The hand was strapped in position with adhesive plaster. The transducer output was amplified and recorded on a Hewlett-Packard recorder.

After steady baseline recordings had been obtained, AH 8165 was injected via a central venous line at three different doses, viz. 0,25 mg/kg, 0,5 mg/kg and 1,0 mg/kg. The following observations were then made:

The time from injection to (*i*) the first detectable diminution of twitch height; (*ii*) the maximal effect on muscle contraction; (*iii*) the first detectable sign of recovery of the twitch response; and (*iv*) the recovery of twitch response to 20% of control values. Direct intra-

arterial pressure recordings were taken in 10 patients. Intra-ocular pressure was measured and recorded in 2 patients scheduled for intra-ocular surgery, by placing an Amsler needle directly into the anterior chamber of the eye.

At the end of the procedure, the effect of the muscle relaxant was reversed by the intravenous administration of 2,5 mg prostigmine and 1,2 mg atropine.

Results

Onset and duration of action: Both the onset and duration of action were broadly dose-related but varied widely (Table I). The speed of onset compares favourably with that of succinylcholine (Fig. 2).

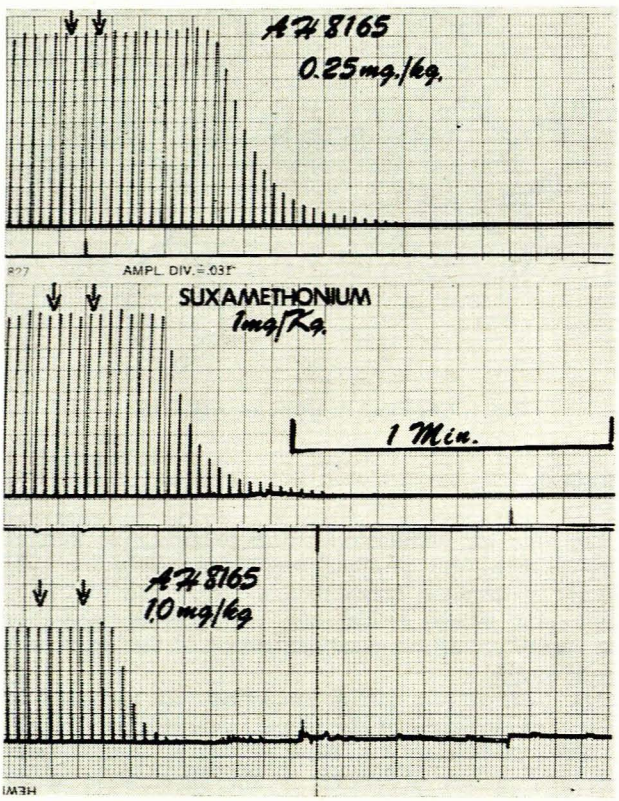

Fig. 2. Comparison of onset of action of AH 8165 with that of succinylcholine.

Intra-ocular pressure: No changes in intra-ocular pressure could be detected during administration of AH 8165, in contrast with the rise in pressure produced by succinylcholine (Fig. 3).

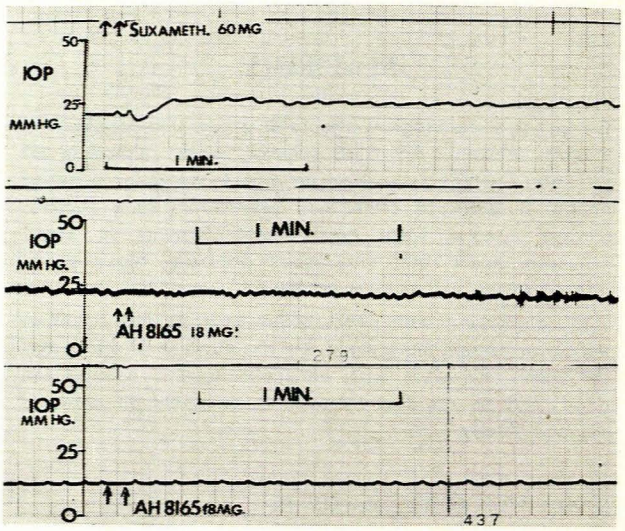

Fig. 3. Effects of succinylcholine and AH 8165 on intra-ocular pressure.

Cardiovascular effects: At a dose of 0,25 mg/kg the relaxant had minimal effects on blood pressure, but caused an increase in pulse rate of 12%. At a dose of 0,5 mg/kg it caused a transient decrease in systolic blood pressure of 12% and a 23% increase in pulse rate (Fig. 4).

Reversibility with anticholinesterase agents: Reversal of neuromuscular blockade was clean and complete in all cases within 3 minutes after injection of prostigmine and atropine (Fig. 5).

COMPARISON

In the second part of the study a clinical comparison of AH 8165 with pancuronium bromide was carried out.

TABLE I. ONSET AND DURATION OF ACTION OF AH 8165

Time from injection		0,25 mg/kg (7 patients)	0,5 mg/kg (7 patients)	1,0 mg/kg (6 patients)
To first detectable action (sec)	Range	14 - 25	12 - 18	6 - 12
	Mean	18,3	13,4	10,0
To maximal effect (sec)	Range	30 - 100	30 - 80	20 - 27
	Mean	51,0	50,7	24,7
To first detectable sign of recovery (min)	Range	4 - 17	5 - 19	22 - 45
	Mean	8,7	13,0	30,0
To 20% recovery (min)	Range	9 - 20	15 - 36	35 - 75
	Mean	13,8	26,3	57,0

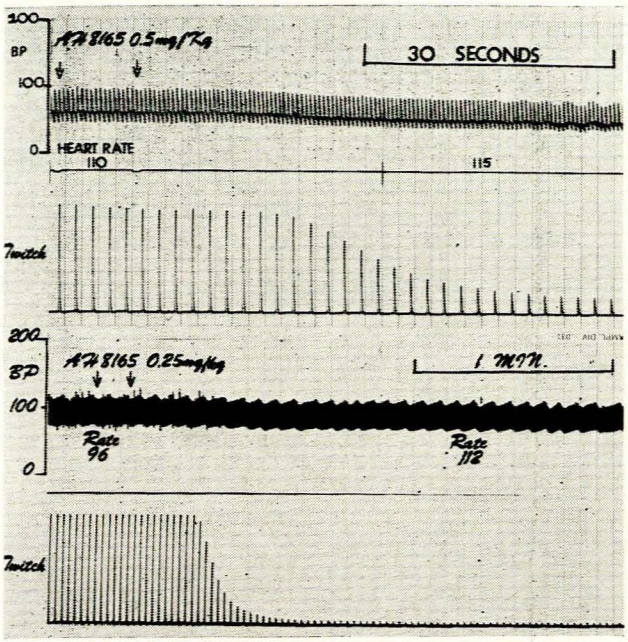

Fig. 4. Typical examples of the effects of AH 8165 on blood pressure and pulse rate.

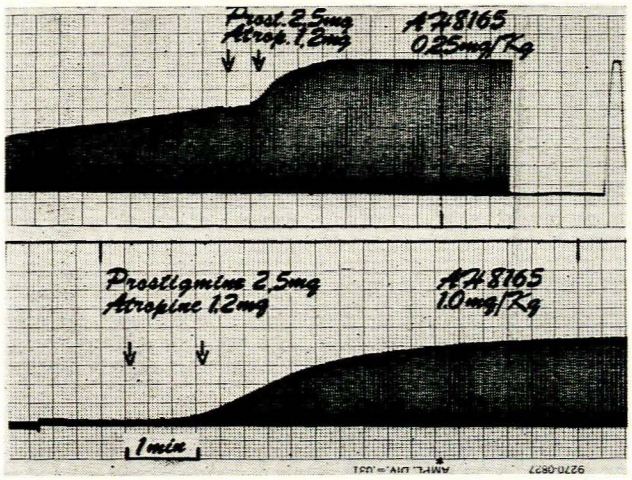

Fig. 5. Examples of the excellent reversal with anticholinesterase of the neuromuscular block due to AH 8165.

Methods

Through experience gained in the first part of the study, it was decided that 0,75 mg/kg would be a reasonable dose for muscle relaxation, and comparable to 0,1 mg/kg of pancuronium. AH 8165 was given to 30 patients and pancuronium bromide to 15 patients.

After pre-oxygenation, anaesthesia was induced with sodium thiopentone, and immediately followed by either 0,75 mg/kg AH 8165 or 0,1 mg/kg pancuronium bromide. All patients were ventilated with pure oxygen until there was minimal resistance to expansion of the chest. Endotracheal intubation was then accomplished. The time from injection until intubation, as well as the ease of intubation, was noted.

Anaesthesia was maintained with oxygen, nitrous oxide and 0,5 - 1% halothane. Increments of AH 8165 (10 - 20 mg) or pancuronium bromide (1 - 2 mg) were given when relaxation appeared to be wearing off. After conclusion of surgery neuromuscular blockade was reversed with 2,5 mg neostigmine and 1,2 mg atropine. The duration of action, degree of relaxation and ease of reversibility were noted.

In 14 patients arterial blood gases and acid-base values were measured immediately before induction and again one hour postoperatively, while the patients were spontaneously breathing room air.

Results

Ease of intubation: Intubation could be accomplished with ease after injection of 0,75 mg/kg of AH 8165 in 26 patients, although movements of the cords, slight bucking or some movements of the extremities did occur in the majority of patients. In 4 patients intubating conditions were regarded as unsatisfactory. These results compared favourably with the intubating conditions attained after the injection of 0,1 mg/kg of pancuronium bromide.

Onset of action: Intubation was carried out at a mean time of 54,1 (± 14,8) seconds after injection of AH 8165. This was considerably shorter than the 150 sec (± 32 sec) necessary after injection of pancuronium bromide before intubation could be carried out.

Duration of action: This was taken as the time from injection until an additional dose was necessary, or until the end of the operation. The duration of action of 0,75 mg/kg was variable, but lasted a mean time of 56 (± 29) min. The duration of action of pancuronium bromide was 69,2 (± 22) min.

Blood gas changes: No residual hypoventilation could be detected one hour postoperatively by means of blood gas analyses (Table II).

TABLE II. PRE- AND POSTOPERATIVE BLOOD GAS VALUES IN 14 PATIENTS BEFORE AND AFTER ADMINISTRATION OF AH 8165

	p_aO_2		p_aCO_2	
	Pre-op.	Postop.	Pre-op.	Postop.
Mean	**76,07**	**74,57**	**34,36**	**32,93**
SD	**7,5**	**11,98**	**2,60**	**2,83**

TABLE III. ACID-BASE CHANGES IN 14 PATIENTS AFTER AH 8165

	pH		Std HCO_3		Base excess	
	Pre-op.	Postop.	Pre-op.	Postop.	Pre-op.	Postop.
Mean	**7,46**	**7,38**	**21,43**	**19,89**	**−2,78**	**−4,78**
SD	**0,18**	**0,21**	**1,42**	**1,86**	**1,78**	**2,34**

Acid-base changes: Small but insignificant decreases in base excess, standard bicarbonate and pH occurred in the immediate postoperative period (Table III).

DISCUSSION

The onset of action of AH 8165 is more rapid than that of pancuronium bromide, and is comparable to that of the fast-acting muscle relaxant, succinylcholine. However, AH 8165 produces less ideal intubating conditions than succinylcholine. To constantly achieve optimal conditions, a higher dose would probably be needed, e.g. 1 mg/kg. If AH 8165 is not used for intubation, a smaller dose of 0,5 mg/kg will provide satisfactory relaxation for surgery. Incremental doses of 10 mg prove adequate when relaxation appears to be wearing off.

The duration of action was not as short in humans as was expected from experimental work, and is similar to that of pancuronium bromide. It is therefore not the solution to the problem of finding a short-acting non-depolarising muscle relaxant. Nevertheless, its rapid onset of action, minimal cardiovascular effects, lack of change in intra-ocular pressure and excellent reversibility with anticholinesterase agents, should prove valuable in anaesthetic practice.

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