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Clinical Pharmacology of Atracurium Besylate (BW 33A): A New Non-depolarizing Muscle Relaxant

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Atracurium, a new non-depolarizing neuromuscular blocking agent, was studied in 70 patients anesthetized with fentanyl, thiopental, and nitrous oxide-oxygen. The dose found to produce 95% twitch inhibition (ED_{95}) was 0.2 mg/kg. The onset time from injection to maximum depression of twitch was 4.0 minutes at this dose; the duration to 95% recovery was 44.1 minutes. Twice the ED_{95} dose (0.4 mg/kg) had an onset time of 1.7 minutes and a duration of 63.5 minutes. No cardiovascular effects were observed in this dosage range. At higher doses (0.5 and 0.6 mg/kg) arterial pressure decreased 13% and 20% and heart rate increased 5% and 8%, respectively. Sixteen patients received at least four successive doses of atracurium. No clinically significant cumulative effect could be shown when recovery from 25% to 75% of control twitch height was compared for initial and final doses in the series. Atracurium spontaneously decomposes at physiologic pH via the Hofmann elimination reaction and may also undergo ester hydrolysis independent of plasma cholinesterase. These proposed pathways of inactivation may explain the lack of cumulative effect and the drug's intermediate duration of action. Based on the results of this study, atracurium offers several clinical advantages and should undergo more extensive clinical trials.

Key Words: NEUROMUSCULAR RELAXANTS: atracurium.

THE CLINICAL need for new neuromuscular blocking drugs of various durations of action (short, intermediate, and long) continues today. One would ideally like these new agents to be non-depolarizing and have high potency, rapid onset, and no cardiovascular side effects. In addition, such new drugs should not release histamine, should lack cumulative properties, should undergo metabolism to pharmacologically inactive and nontoxic metabolites, and should be usable equally well in normal subjects and in patients with renal or hepatic insufficiency. Atracurium besylate (BW 33A), a new non-depolarizing relaxant synthesized and developed by Stenlake (1), appears to possess many of these desirable characteristics. In Britain it has been shown, first in animals by Hughes and Chapple (2) and subsequently in anesthetized patients by Payne and Hughes (3), to be a potent non-depolarizing relaxant devoid of cardiovascular side effects. In addition, atracurium's metabolic pathways may be unique insofar as initial studies suggest that the molecule may decompose at physiologic pH to inactive metabolites by two mechanisms: (*a*) spontaneously by Hofmann elimination, and (*b*) by an enzymatic ester hydrolysis not dependent on plasma cholinesterase (2) (see Fig 1). Atracurium is currently available for clinical trials in this country. The present study was designed to confirm the results of previous investigations and to quantitate in greater detail, time of onset of action, degree of cumulation, if any, and extent of any cardiovascular effects in healthy anesthetized patients during nitrous oxide-narcotic-barbiturate anesthesia.

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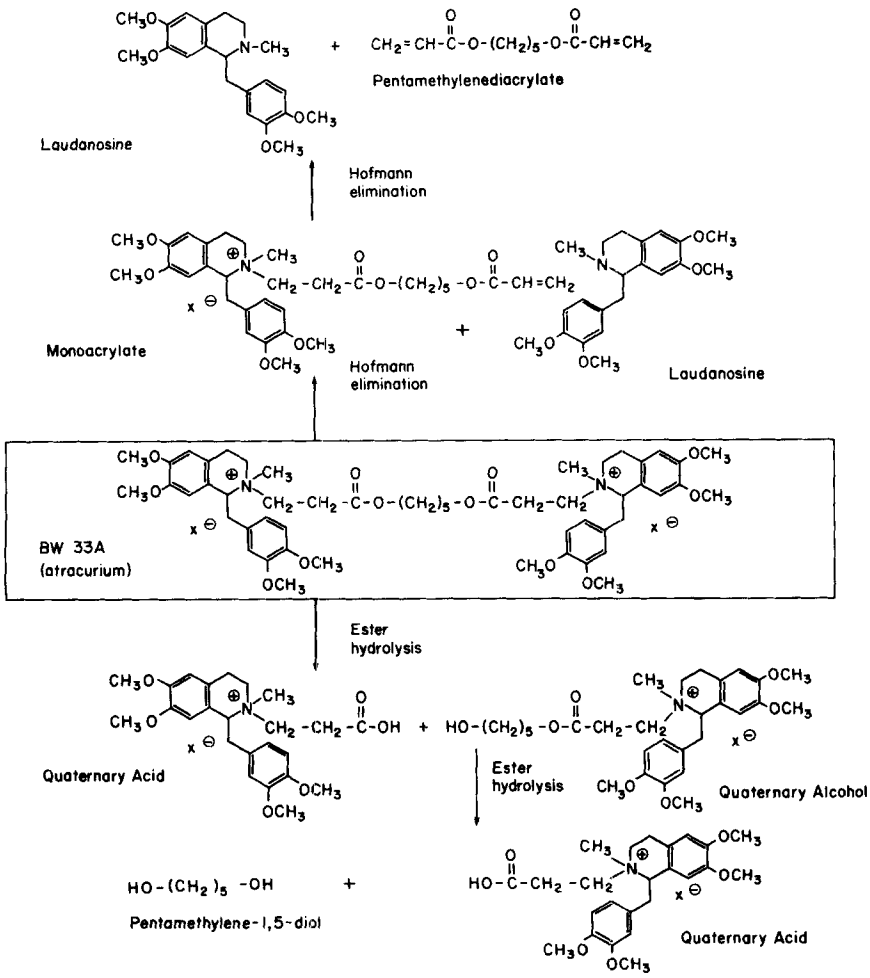

FIG 1. Proposed pathways for inactivation of atracurium by Hofmann elimination reaction and ester hydrolysis.

Methods

The study included 70 patients, 42 men and 28 women, A.S.A. class I, 18 to 58 years of age, who were having elective surgery; all patients gave institutionally approved written informed consent. Before anesthesia, blood samples for determination of dibucaine number and plasma cholinesterase activity were drawn from each subject. This was done to ascertain whether a correlation might exist between the duration of neuromuscular block produced by atracurium and plasma cholinesterase activity. As atracurium is an ester and because in vitro measurements suggest that the drug is not metabolized by plasma cholinesterase (2), this was considered an important aspect of the study.

Fasting subjects were premedicated 1 to 1.5 hours before surgery with oral diazepam, 0.15 mg/kg, and intramuscular morphine, 0.1 mg/kg. Anesthesia was induced with intravenous fentanyl, 4 to 8 μg/kg and thiopental, 5 to 10 mg/kg. Tracheal intubation was accomplished using topical lidocaine. Controlled ventilation was used to maintain normal arterial blood gas tensions. Anesthesia was maintained using nitrous oxide and oxygen (4 L/2 L) and additional thiopental and/or fentanyl as needed. In a few patients it was necessary to use enflurane (0.5% inspired) after recovery from the initial dose of atracurium to maintain adequate levels of anesthesia without administration of high doses of fentanyl or thiopental. These patients were included in analysis of all twitch data.

Heart rate (by tachygraph), radial arterial pressure, esophageal temperature, and electrocardiogram were continuously monitored. Neuromuscular function was monitored by recording responses of the ulnar nerve-adductor pollicis system using 200 to 250 g of resting tension of the thumb. Responses were evoked by repetitive train-of-four stimulation (2 Hz for 2

seconds repeated every 10 seconds) applied to the ulnar nerve as previously described (4), using 22-gauge steel needle electrodes placed subcutaneously at the wrist. Simultaneous recordings of train-of-four responses, arterial pressure, and heart rate were made on a Grass polygraph (model 7B). Train-of-four monitoring was used in this study as an additional indicator that atracurium is a non-depolarizing relaxant which produced fade of the four responses.

Following a stable base line period of 15 minutes, atracurium was administered as a single rapid (5-second) intravenous bolus. Seven separate dosages were used: 0.06, 0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 mg/kg. The time to maximum neuromuscular blockade was measured. Maximal cardiovascular and neuromuscular changes were obtained in the absence of any stimulation, after which surgery began. Recovery of the initial twitch in the train-of-four to 95% of control twitch was measured after each initial dose. Subsequently, greater than 95% neuromuscular blockade was reestablished with an additional 0.2 mg/kg intravenous bolus of atracurium. When this second dose of atracurium was followed by recovery to a point where the initial twitch in the train-of-four response had recovered to 25% of the control height, the blockade was maintained using incremental doses of atracurium, 0.08 mg/kg, given each time the first twitch of the train-of-four had recovered to 25% of control levels. When the duration of surgery was shorter than anticipated and did not allow for spontaneous recovery of the twitch to control levels, residual blockade was antagonized with a mixture of neostigmine and atropine (0.06 and 0.03 mg/kg, respectively) given as a slow (1-minute) intravenous bolus.

Six patients given 0.06 mg/kg of atracurium were also given 0.2 mg/kg of atracurium 1 hour after the initial dose of atracurium had achieved recovery to control twitch height. (No cumulative effect 1 hour after an initial dose of 0.06 mg/kg of atracurium had been observed in a pilot study [n = 4] in which a second dose of 0.06 mg/kg produced a degree of block not differing significantly from that produced by the first dose.) Thus, the total number of bolus doses given at 0.2 mg/kg were 16 (10 patients from the 0.2 mg/kg dosage group plus an additional six patients from the 0.06 mg/kg dosage group).

Statistical comparisons were considered to show significant differences if $p < 0.05$.

Results

A dose-response curve for neuromuscular blockade was constructed using the log-probit method of Litchfield and Wilcoxon (5) for doses giving neuromuscular blockade greater than 0% but less than 100% (dose groups 0.06, 0.1, 0.2, and 0.3 mg/kg). These data were then analyzed by computerized linear regressions yielding the straight-line relationship shown in Fig 2. The dose of atracurium derived from this line necessary to achieve 95% neuromuscular blockade (ED_{95}) was 0.20 mg/kg.

The onset time to maximum blockade was dose related, as shown in Table 1. The times to recovery to 95% of control twitch height are also listed in Table 1. Recovery to 95% of control twitch height for the ED_{95} dose (0.2 mg/kg) averaged 44.1 minutes. Administration of 2 times the ED_{95} (0.4 mg/kg) increased the duration of action by 44% to a mean time of 63.5 minutes, whereas 3 times the ED_{95} (0.6 mg/kg) increased the duration of action only 72% to 75.7 minutes.

Using linear regression analysis, no relationship could be found between plasma cholinesterase activity and duration of neuromuscular blockade. Representative graphs for the 0.2 mg/kg and 0.6 mg/kg doses with r values of 0.19 and 0.05, respectively ($p < 0.05$) are shown in Fig 3.

After recovery from the initial dose of atracurium, neuromuscular blockade was reestablished and then maintained with bolus doses of 0.08 mg/kg of atracurium, administered when patients had recovered to approximately 25% of base line twitch height (i.e., suppression was approximately 75%). This maintenance dose increased suppression to approximately 95% of base line twitch height, which then took

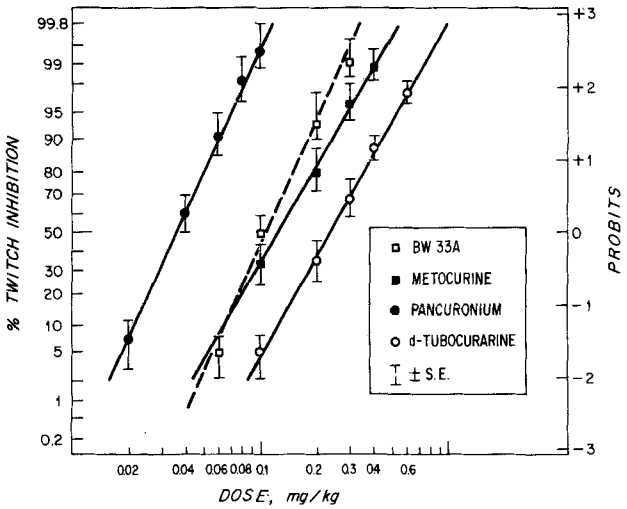

FIG 2. Dose-response curve for atracurium (BW 33A) shown with dose-response curves for *d*-tubocurarine, pancuronium, and metocurine for comparison (4, 6).

TABLE 1

Neuromuscular and Cardiovascular Effects of Atracurium (BW 33A)*

Drug	Dose	N	Block	Onset	95% recovery	25% to 75% recovery	Blood pressure	Heart rate
	mg/kg		*%*		*min*		*% control*	
BW 33A	0.06	10	4.8 ± 9.0/2.9	6.0 ± 1.8/1.04‡	18.4 ± 0.9/0.6§	—	99.0 ± 4.5/1.4	100.0 ± 2.6/0.8
BW 33A	0.10	10	50.9 ± 32.4/10.2	4.4 ± 0.8/0.3	23.2 ± 6.5/2.2	—	99.5 ± 3.4/1.1	99.2 ± 3.1/1.0
BW 33A	0.20	16	94.1 ± 12.1/3.0	4.0 ± 1.96/0.5	44.1 ± 9.6/2.4	12.3 ± 2.6/0.7‖	96.3 ± 11.3/2.8	100.1 ± 4.7/1.2
BW 33A	0.30	10	99.2 ± 1.5/0.5	2.6 ± 0.9/0.3	48.7 ± 2.6/2.4	10.4 ± 3.1/1.0	98.7 ± 3.5/1.1	99.4 ± 3.7/1.2
BW 33A	0.40	10	99.8 ± 0.4/0.1	1.7 ± 0.6/0.2	63.5 ± 8.5/2.7	11.4 ± 2.3/0.7	99.4 ± 3.0/.95	102.3 ± 3.3/1.0
BW 33A	0.50	10	100.0	1.7 ± 0.5/0.1	67.6 ± 17.2/5.4	11.8 ± 2.8/0.9	86.7 ± 19.3/6.1	105.5 ± 5.3/1.7¶
BW 33A	0.60	10	100.0	1.4 ± 0.5/0.2	75.7 ± 10.0/3.2	12.3 ± 2.4/0.7	79.5 ± 17.9/5.7¶	108.3 ± 12.4/3.9¶
dTc†	0.50	16	98.4	3.9 ± 0.9#	137.0 ± 9.6#**	52.2 ± 42#	$p < 0.001$ for 75% recovery	
BW 33A	0.20	16	94.1	4.0 ± 0.5#	38.6 ± 2.5#**	12.3 ± 0.7*		

* Values are means ± SD/SE.

† From Savarese et al (6) and Ali HH, Savarese JJ, Donlon JV, et al. Comparative study between BW(Y100) (compound AA136) "a new short acting nondepolarizing neuromuscular blocking agent," pancuronium, and *d*-tubocurarine. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1975, Hollywood, Florida, pp 195–6. Data included for comparison.

‡ N = 3.

§ N = 2.

‖ N = 14.

¶ $p = < 0.05$ versus control.

Values are means ± SE.

** To 75% recovery.

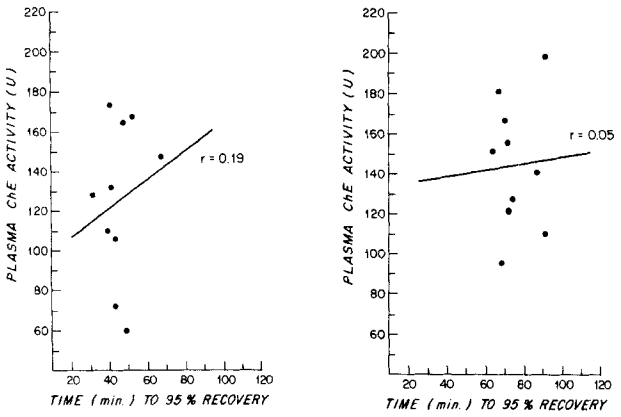

FIG 3. Plasma cholinesterase activity and duration of action of atracurium (BW 33A) ($p > 0.05$), 0.2 mg/kg (left) or 0.6 mg/kg (right) doses, demonstrate no correlation. This helps confirm lack of hydrolysis of atracurium by plasma cholinesterase.

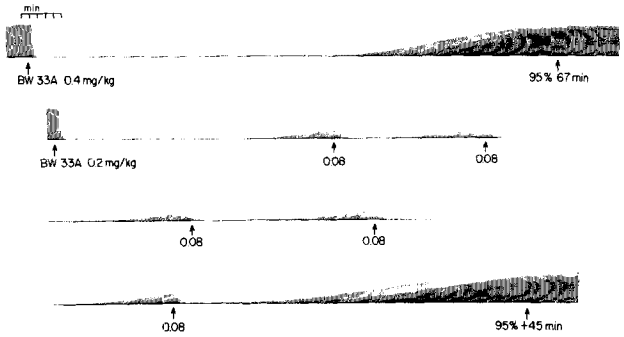

FIG 4. Multiple doses of atracurium (BW 33A) show no clinically important cumulative effect. Each time first twitch of train-of-four had recovered to 25% of control twitch height, a fixed increment, 0.08 mg/kg, of atracurium was given. Degree of neuromuscular blockade and time of recovery were essentially unchanged with each dose.

approximately 16 minutes to recover to 25% of base line. With repeated dosing in this manner (one patient received 12 maintenance doses), there was no evidence to suggest that either the amount or the duration of suppression increased with increasing number of doses.

The 25% to 75% recovery times (time for the first twitch in the train-of-four to recover from 25% of control height to 75% of control levels) for the initial and final doses of atracurium in 16 patients receiving at least four successive doses of atracurium were 11.8 ± 1.19/0.5 (SD/SE) minutes and 13.2 ± 2.5/0.6 minutes, respectively. Correlated *t*-test analysis shows this 1.4-minute difference to be statistically significant ($p < 0.025$). However, this difference is clinically of little importance. Patient 62 in this study received 12 successive doses of atracurium and the 25% to 75% recovery times were 10.0 and 12.3 minutes, respectively, for the initial and final doses. In Fig 4 values for a patient who received multiple doses of atracurium are depicted; note the lack of cumulation and that the train-of-four recovery pattern is the same for the first and last doses.

In eight subjects, residual atracurium blockade was readily antagonized with neostigmine (0.06 mg/kg) and atropine (0.03 mg/kg) as shown in Fig 5. The data are shown in Table 2.

In Table 3 reversal of atracurium by neostigmine is compared with reversal of metocurine (4) for a small group of patients with moderate (64% to 85% twitch depression) neuromuscular blockade. Although the

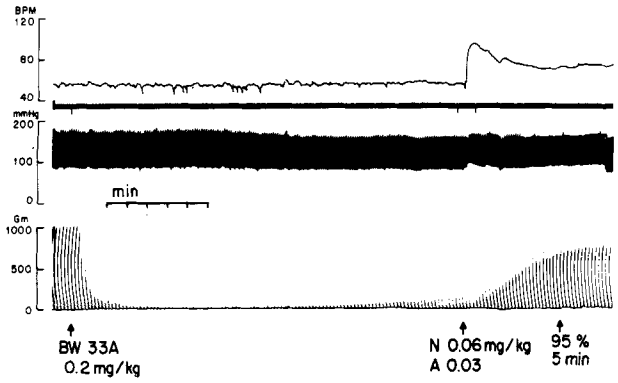

FIG 5. Representative recording show that reversal of atracurium-induced neuromuscular blockade is easily accomplished using neostigmine, 0.06 mg/kg, and atropine, 0.03 mg/kg.

TABLE 2

Antagonism of Atracurium-Induced Neuromuscular Blockade by Intravenous Neostigmine (0.06 mg/kg) and Atropine (0.03 mg/kg)

Twitch height at time of reversal	Time to 95% recovery
% control	*min*
15	10.5
17	4.5
31	5.0
36	9.0
58	5.5
64	5.5
82	3.5
90	0.75

TABLE 3

Comparative Reversals of Atracurium and Metocurine by Neostigmine*

	No. of patients	% twitch inhibition (range)	Neostigmine dose	Time to 98% of control
			mg/kg	*min*
BW 33A	4	75.3 (64–85)	0.06	8.2 ± 1.4
Metocurine†	6	79.0 (75–85)	0.05	7.6 ± 0.4

* Atropine, 0.03 mg/kg, was given to each subject along with the neostigmine.

† From Savarese et al (4).

dose of neostigmine is slightly higher in patients given atracurium, the data suggest that atracurium block is readily reversible and requires similar neostigmine dosage as metocurine reversal. The time required for neostigmine antagonism of this degree of blockade by the two drugs also seems comparable (4).

In Table 1 is seen that at all doses up to and including 2 times the ED_{95} (0.4 mg/kg), atracurium produced no statistically significant changes in arterial pressure or heart rate when paired *t*-test comparisons were made between control values and maximum changes from control values within the first 10 minutes after the administration of atracurium. At 2.5 (0.5 mg/kg) and 3 times (0.6 mg/kg) the ED_{95} dose, there were mild decreases in arterial pressure to 86.7% and 79.5% of control levels, respectively, and mild increases in heart rate to 105.5% and 108.3% of control levels, respectively (Fig 6). Changes in arterial pressure were statistically significant only at the 0.6 mg/kg dose ($p < 0.05$). Heart rate changes were significant for both the 0.5 mg/kg and 0.6 mg/kg doses ($p < 0.05$). These changes were of short duration, the maximal effect occurring 1 to 1.5 minutes after drug injection with a total duration of less than 5 minutes. These cardiovascular changes were associated with slight facial flushing.

Discussion

This study has shown atracurium to be a potent non-depolarizing blocking agent. Atracurium is 2.5 times more potent than *d*-tubocurarine, approximately 50% more potent than metocurine, and one fourth to one third as potent as pancuronium. At doses up to the approximate ED_{95} and ED_{99} (0.2 and 0.3 mg/kg, respectively), the onset of action of atracurium is comparable to other clinically used non-depolarizing relaxants (4, 6) and is dose related.¶ For example, by doubling the dose from 0.2 to 0.4 mg/kg, onset to maximum blockade was shortened from 4.0 to 1.7 minutes, although the total duration of effect increased by only approximately 19 minutes or 44% (Table 1). The time to and ease of intubation were not evaluated in the present study. Payne and Hughes (3), however, showed that in six patients receiving 0.3 mg/kg of atracurium, intubation was easily accomplished within 1.5 to 2.0 minutes, and in six patients given 0.6 mg/kg of atracurium intubation was accomplished within 1 minute. In our study, the onset times to maximum block at 0.3 and 0.6 mg/kg of atracurium were 2.6 and 1.4 minutes, respectively. These onset times suggest that in this dose range of atracurium, intubation might be accomplished within 2 to 3 minutes, or less.

The duration of action of atracurium is relatively short compared with other non-depolarizing agents,

¶ Ali HH, Savarese JJ, Donlon JV, et al. Comparative study between BW(Y100) (compound AA136) "a new short acting non-depolarizing neuromuscular blocking agent," pancuronium, and *d*-tubocurarine. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, Oct 11–15, 1975, Chicago, Illinois, pp 195–6.

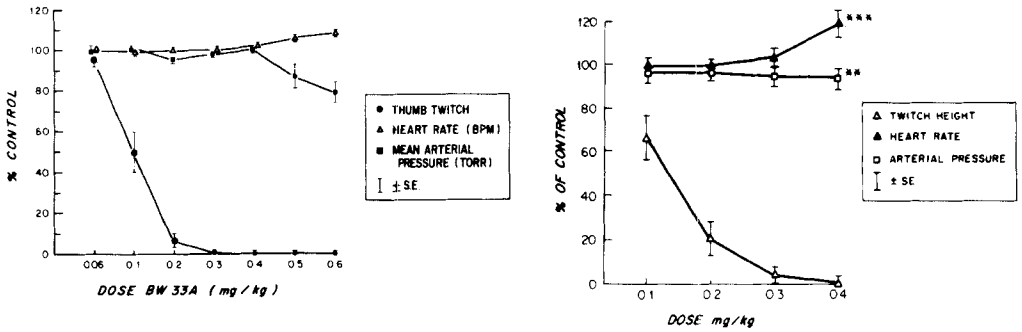

FIG 6. Mean neuromuscular, heart rate, and blood pressure responses to atracurium (BW 33A) at various doses (left). Neuromuscular and cardiovascular effects of metocurine (right) are shown for comparison (4). At equipotent neuromuscular blocking doses, atracurium produces less cardiovascular effects than does metocurine.

lasting approximately one third as long as currently used non-depolarizing drugs. In addition, the consistent pattern of recovery observed after repeated doses of atracurium for maintenance of neuromuscular blockade indicates that it is essentially a noncumulative relaxant.

In those few instances in which antagonism of residual block was necessary, it was easily accomplished by administration of neostigmine and atropine. The speed of reversal was comparable to reversal of metocurine-induced blockade at a similar degree of blockade.

The intermediate duration of action and the lack of cumulative effects of atracurium are probably due to its unique manner of decomposition and metabolism. The molecule was deliberately structured to decompose spontaneously at physiologic pH and normal body temperature by a base-catalyzed reaction termed the Hofmann elimination (1) (Fig 1). In this reaction, the protons on the alpha-carbon atoms (carbon atoms located adjacent to the carbonyl carbon atoms) are acidic. At physiologic pH, a proton can dissociate from the alpha-carbon, leaving an electronegative charge. This allows cleavage of the bond between the beta-carbon (at the end of the intermediate chain of atracurium) and the positively charged nitrogen atom. This cleavage yields an inactive tertiary amine and a diolefin diester as shown in Fig 1. Experiments in animals (Hughes and Chapple [2]), in which the pH was increased from 7.31 to 7.63 by hyperventilation, yielded a significant reduction in the amount and duration of block by atracurium, confirming by inference in vivo occurrence of the Hofmann elimination as this is a base-catalyzed reaction.

An alternate metabolic pathway is also shown in Fig 1. This is believed to be enzymatic hydrolysis of the ester yielding two monoquaternary carboxylic acids and a dialcohol. This enzymatic hydrolysis is probably not dependent on plasma cholinesterase for the following reasons: atracurium is not a choline ester; in vitro hydrolysis in normal human serum and in plasma cholinesterase-deficient human serum is not different (3); and, in the present study, there is no correlation between duration of action of atracurium and plasma cholinesterase activity. It is also interesting to note that in the study of Payne and Hughes (3) in humans, decreasing plasma pH from 7.50 to 7.35 did not increase the duration of action of atracurium, suggesting that the enzymatic ester hydrolysis is functioning more efficiently at the lower pH. Thus, the relative roles of the enzymatic hydrolysis and Hofmann elimination in man have yet to be determined. It may be that each is important, depending on the extracellular pH.

Hughes and Chapple (2) also investigated the role of the liver and kidneys in the elimination of atracurium in cats. The doses of atracurium necessary to produce 50% blockade when given via the jugular vein or the hepatic vein were not significantly different. Further, the ED_{50} was not significantly changed following renal pedicle ligation, nor was the time to recovery significantly prolonged. Thus, in animals neither uptake or metabolism by the liver nor elimination by the kidneys appears to be absolutely necessary for recovery from the effects of atracurium. Further studies in man are needed to confirm these initial findings in animals.

The cardiovascular responses to atracurium as a function of degree of neuromuscular blockade in this study were found, under similar anesthetic conditions, to be more favorable than those associated with metocurine (4), the relaxant currently acknowledged to have the least effect on the cardiovascular system. Payne and Hughes (3) found no significant change in either arterial pressure or heart rate at doses up to 0.6 mg/kg (3 times the ED_{95}), whereas in the present

study, we found slight decreases in arterial pressures and slight increases in heart rate at doses greater than 0.4 mg/kg. The decreases in arterial pressure and the increase in heart rate noted in the present study peaked at 1 to 1.5 minutes, had disappeared within 5 minutes, and were often associated with slight facial flushing. The latter may be due to a relatively weak histamine-releasing property.

The following, in summary, can be said of atracurium: (*a*) It is a potent non-depolarizing neuromuscular blocking agent with approximately one third the duration of action of currently used non-depolarizing relaxants. (*b*) It has a rapid onset of action, especially at 2 times the ED_{95} dosage, which suggests that intubation may be accomplished within approximately 2 to 3 minutes at this dosage. Further clinical studies are needed to confirm this initial clinical impression. (*c*) It has less cardiovascular side effects than metocurine at comparable neuromuscular blocking doses, and has little or no cardiovascular effects at up to 2 times the ED_{95}. By comparison (Fig 4), metocurine begins to show signs of histamine release at approximately 1.3 times the ED_{95}. (*d*) It does not show any clinically important cumulative effects. (*e*) Initial metabolic studies suggest that atracurium undergoes a unique decomposition in plasma to inactive metabolites via the Hofmann elimination (2, 3). It may also undergo ester hydrolysis by an enzymatic pathway that does not involve plasma cholinesterase (3). (*f*) In animals, initial work suggests that atracurium is not dependent on liver metabolism or renal elimination for termination of its action (2). (*g*) Its action is readily antagonized by neostigmine.

For these reasons, atracurium is an intermediate-duration non-depolarizing neuromuscular blocking agent of significant clinical potential and should undergo more extensive clinical trials.

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