

Safety and Efficacy of Atracurium (BW33A) in Surgical Patients Receiving Balanced or Isoflurane Anesthesia

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Atracurium was administered in a dose range of 0.027–0.4 mg/kg and dose-response curves were established for both balanced and isoflurane anesthetic techniques. With balanced anesthesia, ED₅₀ and ED₉₅ were 0.12 and 0.27 mg/kg, respectively, while with isoflurane they were 0.07 and 0.13 mg/kg and the least-squares regression line R² values were 0.71 and 0.64, respectively. With balanced anesthesia there was a significant increase in systolic blood pressure at the 0.04 mg/kg dose ($P = 0.02$), while with isoflurane the systolic and diastolic blood pressures decreased at the 0.3 mg/kg dose ($P < 0.03$). These changes were clinically insignificant.

Atracurium is a potent nondepolarizing muscle relaxant which is potentiated by isoflurane. Its cardiovascular effects appear clinically nonsignificant. There is no evidence of histamine release. (Key words: Anesthesia: balanced. Anesthetics, volatile: isoflurane. Neuromuscular relaxants: atracurium.)

THE CHARACTERISTICS of the ideal muscle relaxant have been described and include, at least, an absence of significant cardiovascular side effects and easy and dependable reversal of the muscle paralysis.¹⁻⁴ The currently available neuromuscular blockers possess varied degrees of potentiation with inhalation agents.⁵ Potentiation of the muscle relaxant by the anesthetic is desirable because it would lessen the dose of relaxant needed and would aid in reversal with discontinuance of the anesthetic agent.

Atracurium (BW33A) was developed at Wellcome Research laboratories as a nondepolarizing neuromuscular-blocking agent. Studies in laboratory animals have demonstrated that it is a potent agent of medium duration and is readily reversed with anticholinesterase. The autonomic effects of the drug appear to be minor in that vagal blockade was noted only at doses more than eight times those needed for complete paralysis.⁶ There were minimal sympathetic effects. Histamine release is also minimal and occurs only at doses much higher than the full paralyzing doses.

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The purpose of this study was to evaluate the efficacy, potency, and safety of atracurium in humans and establish the degree of interaction with isoflurane.

Materials and Methods

Sixty-five, ASA 1 or 2 patients, aged 18–60 years, weighing 40–110 kg, and scheduled to undergo low to moderate risk surgical procedures were admitted to the study and their consent to participate was obtained. The protocol for the study was approved by the institution's human research committee. The patients were divided into two groups. Group A (25 patients) were given doses of atracurium ranging from 0.06–0.4 mg/kg after establishing a near steady state of balanced anesthesia using thiopental, N₂O, O₂, and fentanyl. Group B (40 patients) were given atracurium in doses ranging from 0.027–0.3 mg/kg after establishing a near steady state of anesthesia using N₂O, O₂ (60–40%), and isoflurane (0.60–0.65% end-tidal) to total 1.25 MAC. Isoflurane's end-tidal concentration was measured by mass spectrometry. Several dose regimens of atracurium were used in each group to establish a dose-response curve. Patients were excluded from the study if they 1) had a personal or family history of malignant hyperthermia; 2) had a history of unusual sensitivity to neuromuscular-blocking agents; 3) had a history of alcohol or drug abuse; 4) had evidence of psychiatric, neuromuscular, severe cardiovascular disease, or impaired renal or liver function; 5) had a history of asthma; 6) had exposure to aminoglycoside antibiotics, quinidine, lidocaine, or trimethaphan within 48 h of the study; 7) had been exposed to antihistamine or antidepressants within one week of the study; 8) had ECG abnormalities observed prior to drug administration; and 9) had child-bearing potentials.

Premedication consisted of 50–150 µg/kg morphine and 3–4 µg/kg scopolamine intramuscularly and/or 150 µg/kg diazepam orally, and was administered 45–90 min prior to surgery. In the operating room suite, lactated Ringer's solution with 5% dextrose was administered in a peripheral arm vein via an indwelling catheter. The ECG was monitored continuously. Blood pressure was measured every minute with an electronic oscillometer (Dinamap®). The thumb of a restrained arm was attached to a force displacement transducer to measure and record twitch response of the adductor pollicis

muscle to ulnar nerve stimulation. The ulnar nerve was stimulated via two 25-gauge subcutaneous needles using a Grass® stimulator delivering square wave pulses at 0.2 Hz, 0.2 ms, and supramaximal voltage (at least 20 V above maximum). The elicited response was recorded on a polygraph. Respiration was either assisted or controlled to achieve normal blood gases. Temperature was monitored by an oral or axillary thermistor and maintained at $36.5 \pm 0.5^\circ \text{C}$. Anesthesia was induced with 3–4 mg/kg thiopental and maintained with a 60% N₂O and 40% O₂ mixture and either a narcotic, morphine, or fentanyl or isoflurane. After reaching a near steady state with either technique (not less than 15 min at 1.25 MAC in the case of isoflurane) the predetermined dose of atracurium was injected as a bolus in a free flowing iv. The following variables were recorded: 1) time from injection to development of maximum block; 2) duration of maximum block (from maximal block to first evidence of recovery); 3) time for recovery from 25–75% of control twitch height; 4) time to 95% and full recovery of twitch height; 5) pulse rate, systolic, diastolic, and mean arterial blood pressure (every minute); and 6) all of these same variables following subsequent doses of atracurium given after at least 95% recovery from the previous dose.

Endotracheal intubation, when indicated, was performed at least 10 min after development of maximum blockade and following the termination of collection of all hemodynamic data. In the latter case, an evaluation of intubating conditions was made and graded as 1) excellent—easy without coughing or bucking; 2) good—easy with slight bucking and/or coughing; or 3) poor—achieved with moderate coughing or bucking and accompanied by vocal cord movement.

Reversal of neuromuscular blockade was attempted if there was residual block at the end of the surgical

procedure as indicated by a train-of-four ratio less than 0.8 and a nonsustained response to a 50-Hz tetanic stimulus delivered for 3 s. Atropine, 1.0 mg, and neostigmine in increments of 0.5 mg were then administered to achieve reversal of block documented by a train-of-four ratio greater than 0.8 or sustained tetanic response to 50 Hz stimulation for 3 s.

Patients were discharged from the recovery room at least two hours after the termination of surgery with no clinical evidence of any residual muscle relaxant effect.

Statistical analysis of the data collected was performed by 1) analysis of variance within each anesthetic technique group of patients, and 2) Student's unpaired *t* test to compare the two groups of patients.⁷ Differences were considered to be significant when $P < 0.05$. The log-probit method of Litchfield and Wilcoxon⁸ was used to construct the dose-response curve and a computerized analysis of the dose-response curve was performed by least-squares linear regression analysis to yield a straight line relationship.

Results

The two groups studied were not significantly different regarding age, height, or weight.

In each group atracurium produced a dose-dependent neuromuscular block. When the data were plotted as a log-probit relationship the dose-response lines did not differ from parallel. The R² values for balanced and isoflurane anesthesia were 0.71 and 0.64, respectively (fig. 1). In those patients given balanced anesthesia 0.06 mg/kg atracurium produced a $12.0 \pm 3.5\%$ depression of twitch height while doses of 0.10 mg/kg, 0.20 mg/kg, and 0.30 mg/kg produced neuromuscular blocks of 32.2 ± 14.4 , 83.8 ± 3.8 , and $99.8 \pm 0.2\%$, respectively. Under isoflurane anesthesia, doses of 0.027,

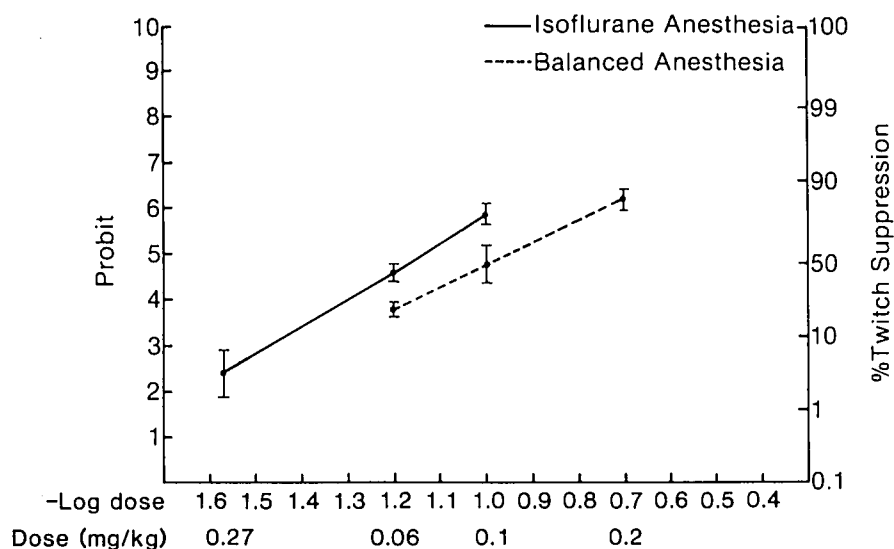


FIG. 1. Log-probit plot comparing dose-response curves for atracurium under balanced and isoflurane anesthesia. Linear regression analysis reveals an R² for balanced = 0.71 and for isoflurane 0.64. Values are means \pm SE; n balanced = 5; n isoflurane = 10.

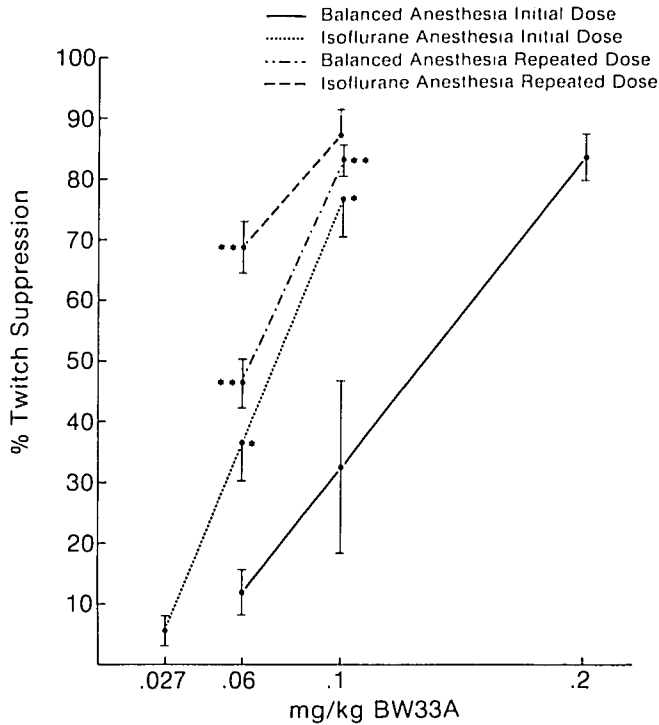


FIG. 2. Twitch suppression as a function of dose of atracurium administered under balanced or isoflurane anesthesia for initial and repeated doses. Repeated doses were given after twitch tension had recovered to at least 95% of control. The increased magnitude of block suggests cumulation of effect. Values are means \pm SE; n initial balanced = 5; initial isoflurane = 10; repeat balanced 0.06 mg/kg = 9; repeat balanced 0.1 mg/kg = 19; repeat isoflurane 0.06 = 5; and repeat isoflurane 0.1 mg/kg = 9. *Isoflurane compared with balanced anesthesia, $P < 0.05$. **Repeat dose compared with initial dose, $P < 0.05$.

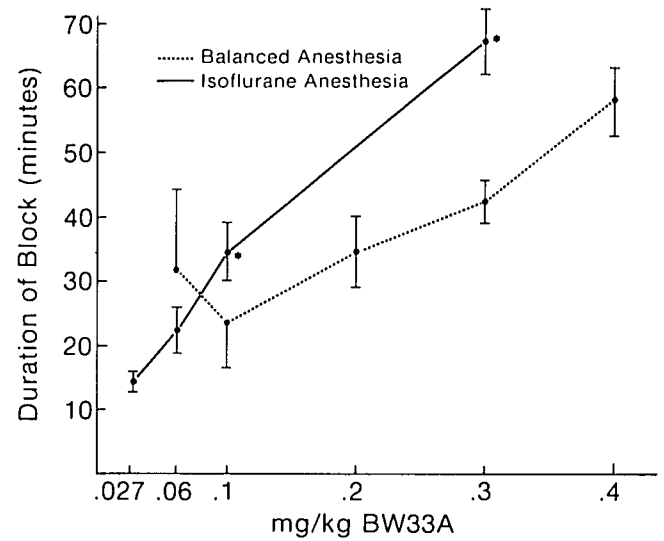
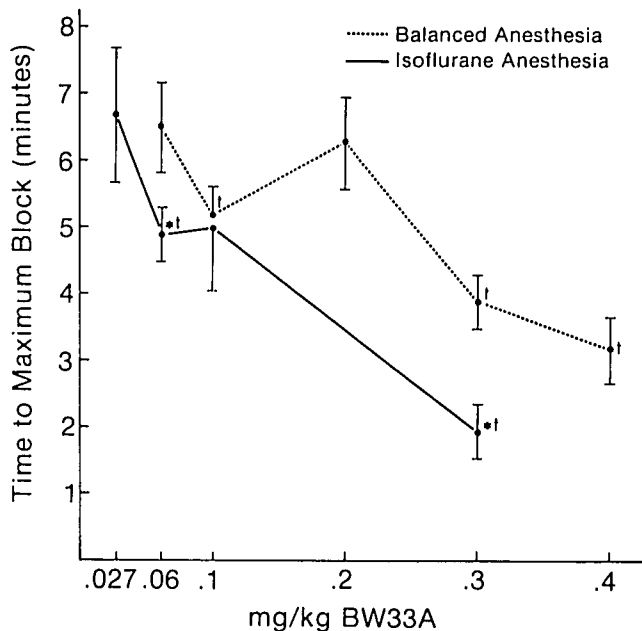


FIG. 4. Duration of neuromuscular block produced by atracurium in relation to dose and anesthetic techniques. There is a dose-related increase of duration of the block with both techniques. Isoflurane significantly prolongs the duration more than balanced anesthesia ($*P < 0.05$). n balanced = 5, and isoflurane = 10. Values are means \pm SE.

0.06, 0.10, and 0.30 mg/kg produced blocks of 5.6 ± 2.2 , 36.7 ± 6.4 , 76.4 ± 6.3 , and $99.9 \pm 0.1\%$, respectively (fig. 2). When comparing the effects of equal drug doses between the two anesthetic techniques, a significantly greater degree of neuromuscular block was produced in those patients anesthetized with isoflurane. This increased block is quantified in the estimated ED₅₀ and ED₉₅. For balanced anesthesia these values were 0.12 and 0.27 mg/kg, while for isoflurane they were 0.07 and 0.13 mg/kg, respectively ($P < 0.01$) (fig. 2).

There was a dose-related decrease in time to onset of maximal block with both anesthetic techniques ($P < 0.01$). Additionally, when using equal doses of atracurium the speed of onset of the neuromuscular block was more rapid in those patients anesthetized with isoflurane at doses of 0.06 and 0.30 mg/kg ($P < 0.05$) but not at 0.10 mg/kg (fig. 3).

The duration (from injection to 95% recovery) of neuromuscular block produced by atracurium was dose-dependent ($P < 0.01$) with both anesthetic techniques (fig. 4). The duration of block was increased by about



FIG. 3. Time required for development of maximum neuromuscular blockade related to dose and type of anesthesia. With increasing dose the time to maximal block is significantly decreased ($P < 0.05$). Development of maximal block is more rapid ($*P < 0.05$) with isoflurane compared with balanced anesthesia at comparable doses. n balanced anesthesia = 5, and isoflurane = 10. Values are means \pm SE.

50% with isoflurane when compared with balanced anesthesia. Thus, the duration of the block produced by 0.1 mg/kg atracurium was increased from 23.6 ± 6.9 min with balanced anesthesia to 34.6 ± 4.8 min with isoflurane (*P* < 0.01). Likewise, a 0.30 mg/kg dose produced a neuromuscular block which was prolonged from 42.3 ± 3.4 min with balanced anesthesia to 67.3 ± 5.9 min for isoflurane anesthesia (*P* < 0.01).

Recovery from neuromuscular blockade (25% to 75% of control twitch height) was independent of the initial dose of atracurium administered. Under balanced anesthesia the time to recovery from 25% to 75% of twitch were 11.8 ± 1.1, 10.6 ± 1.7, and 10.7 ± 0.6 min with doses of 0.2, 0.3, and 0.4 mg/kg atracurium, respectively. These recovery times were not significantly different from each other. With isoflurane anesthesia the 25% to 75% recovery times were 13.5 ± 1.5 and 15.1 ± 2.4 min for atracurium doses of 0.1 and 0.3 mg/kg, respectively. Again, these are not significantly different. However, when comparing the recovery rate from 0.3 mg/kg atracurium between the two anesthetic techniques, there was a slight but significant decrease in recovery rate with isoflurane (*P* < 0.05).

TABLE 1. Maximum Vital Sign Changes from Pre-injection Values after Initial Atracurium Dose: Balanced Anesthesia

Dose (mg/kg)	Variable	N	Pre-injection (Mean ± SE)	Post-injection (Mean ± SE)
0.060	Blood pressure (mmHg)			
	Systolic	5	114 ± 5	118 ± 8
	Diastolic	5	60 ± 5	70 ± 4
	Mean arterial	5	82 ± 4	87 ± 7
	Heart Rate (beats/min)	5	53 ± 4	56 ± 3
0.100	Blood pressure (mmHg)			
	Systolic	5	114 ± 2	114 ± 5
	Diastolic	5	59 ± 3	65 ± 3
	Mean arterial	5	80 ± 6	81 ± 4
	Heart rate (beats/min)	5	65 ± 5	60 ± 5
0.200	Blood pressure (mmHg)			
	Systolic	5	108 ± 6	97 ± 4
	Diastolic	5	63 ± 3	56 ± 3
	Mean arterial	5	80 ± 5	70 ± 3
	Heart rate (beats/min)	5	55 ± 6	50 ± 3
0.300	Blood pressure (mmHg)			
	Systolic	5	112 ± 5	113 ± 8
	Diastolic	5	58 ± 6	56 ± 4
	Mean arterial	5	76 ± 4	80 ± 7
	Heart rate (beats/min)	5	62 ± 7	69 ± 8
0.400	Blood pressure (mmHg)			
	Systolic	5	104 ± 5	122 ± 3*
	Diastolic	5	61 ± 6	60 ± 7
	Mean arterial	5	76 ± 6	80 ± 4
	Heart rate (beats/min)	5	60 ± 6	59 ± 5

**P* < 0.05.

TABLE 2. Maximum Vital Sign Changes from Pre-injection Values after Initial Atracurium Dose: Isoflurane Anesthesia

Dose (mg/kg)	Variable	N	Pre-injection (Mean ± SE)	Post-injection (Mean ± SE)
0.027	Blood pressure (mmHg)			
	Systolic	10	106 ± 4	103 ± 4
	Diastolic	10	51 ± 2	51 ± 3
	Mean arterial	10	71 ± 3	70 ± 3
	Heart rate (beats/min)	10	59 ± 2	59 ± 3
0.060	Blood pressure (mmHg)			
	Systolic	10	105 ± 5	114 ± 5
	Diastolic	10	55 ± 2	60 ± 5
	Mean arterial	10	75 ± 3	77 ± 4
	Heart rate (beats/min)	10	68 ± 5	70 ± 5
0.100	Blood pressure (mmHg)			
	Systolic	10	108 ± 3	109 ± 6
	Diastolic	10	66 ± 6	65 ± 5
	Mean arterial	10	82 ± 5	83 ± 5
	Heart rate (beats/min)	10	60 ± 3	63 ± 4
0.300	Blood pressure (mmHg)			
	Systolic	10	107 ± 4	100 ± 4*
	Diastolic	10	61 ± 3	55 ± 3*
	Mean arterial	10	79 ± 4	74 ± 4
	Heart rate (beats/min)	10	72 ± 3	73 ± 4

**P* < 0.05.

When repeated doses of 0.06 and 0.1 mg/kg atracurium were administered following at least 95% recovery of twitch tension the time to maximal block was significantly shorter at both drug doses (*P* < 0.05) with isoflurane but not balanced anesthesia when compared with the initial dose. With the same drug doses the degree of block was significantly greater compared with the same initial dose with balanced anesthesia (*P* < 0.01) at both drug doses. With isoflurane, a significant difference was seen only at the 0.06 mg/kg dose (*P* < 0.01) (fig. 2).

Reversal of residual neuromuscular block was accomplished readily using 1.0 mg atropine and neostigmine in increments of 0.5 mg every 3 min until complete electrical reversal evidenced by a train of four ratio greater than 0.8 or a sustained response to a 3-s, 50-Hz tetanic stimulus was achieved.

Under balanced anesthesia, there was a statistically significant increase in systolic blood pressure following the 0.4 mg/kg dose (*P* = 0.02) (table 1). Under isoflurane anesthesia there was a statistically significant increase in systolic blood pressure following the 0.06 mg/kg dose (*P* = 0.02) and statistically significant decrease in systolic and diastolic blood pressure following the 0.3 mg/kg dose (*P* = 0.02 and 0.03, respectively) (table 2). No allergic phenomena were noted as manifested by erythema, urticaria, or bronchospasm.

Endotracheal intubating conditions were rated as ex-

cellent following doses of 0.3 and 0.4 mg/kg of atracurium at a time when the patient was near a steady state of general anesthesia and at least 10 min after drug administration.

Discussion

In this study, a dose-response relationship was established for the neuromuscular actions of atracurium in humans under either balanced or isoflurane anesthesia. With this drug, the time to development of maximal block and its degree and duration are dose-dependent. In this respect, atracurium appears to be similar to other neuromuscular-blocking drugs.

In the statistical analysis only those patients developing more than 0% but less than 100% block were used. The log-probit method of Litchfield and Wilcoxon⁸ was used to construct the dose-response curve. The log-probit relationship produces a better fitting straight line than the linear regression analysis transported from arithmetic scales especially at the extremes of the response ranges. A computerized system analyzed the data further to produce the straight line, dose-response curve.

The finding in this study of a dose-dependent shortening of the time of development of neuromuscular blockade is in agreement with the work of Payne and Hughes.⁹ Although they used halothane as the anesthetic agent, the onset of atracurium-induced blockade (0.3 mg/kg) was the same (1.9 min) as our finding with isoflurane. However, the two studies differed in the duration of such blockade. While they reported that a 0.3 mg/kg dose produced a block of 44 min duration, we found that under balanced anesthesia the duration was 42 min and that under isoflurane it was prolonged (67 min). This discrepancy may be attributed to the fact that they monitored peak tetanic response while we used twitch responses and that different anesthetic agents were used.

That the total dose of a neuromuscular-blocking drug administered affects the rate of onset as well as the magnitude of the block is seen in the observations of Brown *et al.*¹⁰ with pancuronium. These authors noted that increasing drug doses decreased the time required to produce 100% block of indirectly elicited twitch.

The duration of block produced by atracurium as defined by the time from injection to 95% recovery was dose-related and very predictable. This predictability may be of considerable clinical utility permitting the anesthesiologist to more accurately judge the dose of relaxant needed to provide a given duration of relaxation. The moderate duration of action of the drug would make it useful for short as well as lengthy procedures.

Although the duration of action was dose-dependent,

the time required for 25 to 75% recovery was not. This aspect of the action of neuromuscular blocking drugs has not been well studied and may be unique to atracurium.

In vitro halothane and isoflurane potentiate the effects of neuromuscular blocking agents to the same extent.¹¹ In contrast, *in vivo*, isoflurane produces more potentiation than does halothane.¹² This was ascribed to an increased muscle blood flow produced by isoflurane. This hypothesis can explain the more rapid onset and greater block with isoflurane seen in this study. Recovery from neuromuscular block might be influenced by various factors. If redistribution is an important factor in terminating the action of atracurium as it is with other nondepolarizing drugs, then the increased blood flow should enhance the rate of recovery. Contrary to this, an increasing concentration of isoflurane at the junctional region during the period of neuromuscular block would tend to enhance the effect of the drug. As a third alternate, even other mechanisms of drug action at the neuromuscular junction may be involved. This has been investigated partially in studies demonstrating that neither halothane nor isoflurane depress either twitch tension or acetylcholine release in an indirectly stimulated frog nerve-muscle preparation.¹³

The administration of repeat doses of atracurium usually resulted in a block that was faster in onset and more profound than that seen with the initial dose of the same magnitude. We interpret this as suggesting some degree of cumulative effect. This needs further evaluation.

The cardiovascular safety of atracurium is suggested by the absence of any observed clinically significant alteration of mean arterial blood pressure, heart rate, or ECG with any of the doses studied with either anesthetic technique. This is supporting evidence that the drug has little autonomic stimulating or blocking effect. These observations are similar to those of Payne and Hughes.⁹ More direct studies of the cardiovascular effects of the drug are being performed currently.

There appeared to be no clinically significant histamine release with atracurium in this study as evidenced by the absence of allergic skin manifestation, bronchospasm, or severe hypotension.

From this study it can be safely concluded that atracurium is a potent nondepolarizing muscle relaxant of moderate duration. In clinical doses, it has no cardiovascular side effects. There is no clinical evidence of histamine release. It is readily reversible with the usual anticholinesterase drugs. The effect of atracurium is potentiated by isoflurane compared with balanced anesthesia in that patients require approximately one-half the dose of atracurium to attain a given degree and duration of block.

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