Anesthesiology
1996; 85:169–77

Comparative Pharmacology of Cisatracurium (51W89), Atracurium, and Five Isomers in Cats

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Background: **Atracurium has four chiral centers and the marketed product is a mixture of ten optical and geometric isomers. Six of the isomers were prepared and evaluated for neuromuscular blocking activity and autonomic effects in anesthetized cats. This study reports the comparative pharmacology of the six isomers and atracurium that led to the selection of one isomer, cisatracurium (Nimbex, 51W89) for clinical development.**

Methods: **Purpose bred cats, anesthetized with alpha-chloralose (80 mg/kg) and pentobarbital sodium (7 mg/kg) administered intraperitoneally, were used in this study. Neuromuscular blocking effects were assessed from the effects on the tibialis anterior twitch evoked at 0.15 Hz. Inhibition of the autonomic nervous system was assessed from the effects on the nictitating membrane contraction, in response to preganglionic sympathetic nerve stimulation and the bradycardia/vasodepressor responses to vagal nerve stimulation. Cardiovascular effects and plasma histamine concentrations were determined after a bolus injection of cisatracurium or atracurium.**

Results: **Like atracurium, all six isomers produced dose-dependent neuromuscular block (NMB). The calculated ED_{95} NMB values varied approximately tenfold (43 ± 2 μg/kg–488 ± 56 μg/kg). The "R-series" isomers were more potent than the corresponding "S series" isomers. With the exception of the S,Trans-S′,Trans isomer, the NMB effects, *i.e.,* onset times (range 2.6 ± 0.2 min to 4.7 ± 0.3 min) and total durations (range 9.9 ± 1.4 min to 14 ± 0.9 min), of the other five isomers were very similar to that of atracurium. The former isomer had a relatively short duration of action. The 25–75% recovery times after cisatracurium at 1× ED_{95} (4.4 ± 0.4 min), 4× ED_{95} (4.5 ± 0.4 min), and continuous infusions lasting at least 60 min that maintained 95–99% NMB (4.8 ± 0.4 min) indicated a noncumulative effect. The vagal ID_{50}: NMB ED_{95} ratios for atracurium and the six isomers ranged from 2 to 27. The sympathetic ID_{25}: NMB ED_{95} ranged from 2.7 to 60. Atracurium and all of the isomers, except cisatracurium, produced cardiovascular effects after intravenous bolus administration at large doses (700–4,800 μg/kg). In contrast to atracurium, there were no changes in plasma histamine concentrations associated with the administration of doses of cisatracurium equivalent to 60× the NMB ED_{95} (62 ± 8 μg/kg).**

Conclusions: **Cisatracurium has neuromuscular blocking effects identical to those of atracurium, is more potent, and does not produce cardiovascular effects or increase plasma histamine concentrations. (Key words: Animals: cat. Neuromuscular relaxants, neuromuscular blocking agents: atracurium; cisatracurium (51W89).**

ATRACURIUM (Tracrium, Glaxo Wellcome, Research Triangle Park, NC) is an intermediate-duration, nondepolarizing neuromuscular blocking agent introduced into clinical anesthesia in the early 1980s. Atracurium has four chiral centers in its bis-benzylisoquinolinium structure; however, because of molecular symmetry, the 16 theoretical isomers are reduced to a mixture of 10 optical and geometric isomers.[1] The isomers are denoted by defining the absolute stereochemistry (R or S) at C-1 of the tetra-hydropapaverine ring and the relative *cis* or *trans* geometry of the bulky dimethoxybenzyl and alkyester groups at C-1 and N-2, respectively. The ratios of the Cis-Cis, Cis-Trans, and Trans-Trans isomers is approximately 10:6:1; corresponding to about 50–55% Cis-Cis, 35–38% Cis-Trans, and 6–7% Trans-Trans isomers, respectively.[1,2] Several authors have reported on the separation of the isomers,[1,2] the pharmacokinetics,[3] and the neuromuscular blocking potencies.[1] All of the above studies were performed with groups of optical isomers, *e.g.,* the Trans-Trans isomer group contained isomers designated R,Trans-

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Received from the Division of Pharmacology, The Burroughs Wellcome Foundation, Research Triangle Park, North Carolina. Submitted for publication July 3, 1995. Accepted for publication March 6, 1996. Presented in part at annual meeting of the American Society of Anesthesiologists, Washington, D.C., October 1993.

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R′,Trans; R,Trans-S′,Trans; and S,Trans-S′,Trans. Interestingly, Tsui *et al.* observed differential rates of enzyme hydrolysis and speculated that the identification and isolation of atracurium isomers that are hydrolyzed rapidly may allow the development of a neuromuscular blocking agent with similar kinetics to succinylcholine. To date, no data on the comparative pharmacologic properties of the individual isomers of atracurium have been reported. Six of the component isomers contained in atracurium have been prepared in quantities sufficient for testing in experimental animals. Unfortunately, the other four isomers could not be synthesized individually or separated from the atracurium mixture. This study was undertaken to determine the neuromuscular blocking profiles, the effects on the autonomic nervous system, and the potential of atracurium and the six available isomers to produce cardiovascular effects in anesthetized cats.

Methods

All experimental protocols used in these experiments were approved by our institutional Animal Care Use Committee and were in accordance with the United States Public Health Service, National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. These experiments were performed in purpose bred (Harlan Sprague Dawley, Indianapolis, Indiana) male cats, weighing 2.9–5.2 kg. All animals were anesthetized with a mixture of 7 mg/kg intraperitoneal pentobarbital sodium and 80 mg/kg intraperitoneal α-chloralose. Adequate levels of anesthesia were maintained with supplemental doses of α-chloralose (5–10 mg/kg) administered intravenously *via* a cannula in the femoral vein. The trachea was cannulated and the animals lungs were ventilated with room air *via* a Harvard Apparatus (South Natick, MA) respiration pump. Arterial blood pressure was measured from a cannula in the femoral artery connected to a Statham P23 transducer (Gould, Oxnard, CA). Heart rate was determined from the electrocardiogram (lead II) using a Grass Model 7P44 tachograph (Quincy, MA). The left hind limb was rigidly mounted and the tibialis tendon was isolated and attached to a Grass FT.03 force displacement transducer. After sectioning the sciatic nerve trunk at the hip, the peroneal nerve was mounted on platinum electrodes. Stimuli of 0.2-ms duration and at a supramaximal voltage were applied to the nerve at the rate of 0.15 Hz using a Grass S88 stimulator. Twitch tension in the tibialis anterior was recorded with a resting tension of 50 g. The right vagus nerve and the right sympathetic trunk were decentralized. Stimulating electrodes were placed on the distal stump of the vagus and on the preganglionic fibers of the sympathetic trunk. Ten-second trains of square waves at 20 Hz, 0.5-ms duration, and supramaximal voltage were applied to the nerve at 5-min intervals. The contractions of the right nictitating membrane at a resting tension of 5 g were recorded *via* a Grass FT.03 transducer. All recordings were made simultaneously for tibialis anterior twitch, electrocardiogram, arterial blood pressure, nictitating membrane contraction, and heart rate on a Grass Model 7 polygraph. Esophageal temperature was monitored with a Yellow Springs thermistor probe and core temperature was maintained between 37° and 38°C with radiant heat. All nerves and tendons were kept moist with mineral oil or mineral oil-soaked cotton. At the end of the experiments, cats were killed with intravenously administered saturated potassium chloride and/or pentobarbital sodium.

Onset of neuromuscular block was measured as the time from injection to maximal twitch depression, and total duration was measured as time from injection to return to 95% of control twitch height. Recovery times were measured for 5–95% and 25–75% return of twitch height. The dose-response curve for neuromuscular block was estimated by linear regression of probit values corresponding to the percentage depth of neuromuscular block.[4] Because of the strong similarity of the neuromuscular blocking effects, especially onset times and total durations observed with cisatracurium, atracurium, and vecuronium, additional comparative experiments were performed with cisatracurium, atracurium, and vecuronium. Pharmacodynamic trend analysis and statistical comparisons of neuromuscular ED values were made by analysis of variance with the Bonferroni correction for multiple comparisons with significance accepted at $P < 0.05$.[5]

Dose-response curves for inhibition of neuromuscular, vagal (parasympathetic), and sympathetic ganglionic function were determined for each animal. The dose-response curves were determined as follows: for neuromuscular blockade a dose-response curve (at least three doses) was constructed for each animal. The animal was allowed to remain stable between doses for 60 min after return of twitch baseline. Mean ED_{25}, ED_{50}, and ED_{95} values (doses that decreased the tibialis twitch height 25%, 50%, or 95%, respectively) were calculated from the individual log-probit dose-response curves. Parasympathetic dose-response curves were

Table 1. Neuromuscular Blocking Effects Determined in Anesthetized Cats

Compound	Calculated ED_{95}* (μg/kg)	Onset† (min)	Total Duration‡ (min)	Recovery Time (min)	
				5–95%	25–75%
S,Trans-S', Trans (34W89)	488 ± 56	1.8 ± 0.1	7.8 ± 0.5	5.6 ± 0.5	2.2 ± 0.2
S, Cis-S', Trans (35W89)	162 ± 6	2.6 ± 0.2	9.9 ± 1.4	6.8 ± 1.2	2.8 ± 0.5
S, Cis-S', Cis (36W89)	88 ± 8	3.0 ± 0.3	11.2 ± 0.7	7.1 ± 0.6	3.0 ± 0.2
R, Trans-R', Trans (49W89)	79 ± 6	3.5 ± 0.2	11.5 ± 1.0	6.6 ± 0.9	2.8 ± 0.4
R, Cis-R', Trans (50W89)	43 ± 2	4.7 ± 0.3	14.0 ± 0.9	7.8 ± 1.1	3.6 ± 0.5
Cisatracurium (51W89)	62 ± 8	3.7 ± 0.1	12.7 ± 0.9	8.5 ± 1.0	3.8 ± 0.4
Atracurium	92 ± 10	4.1 ± 0.2	12.7 ± 1.4	7.4 ± 1.0	3.0 ± 0.5
Vecuronium	28 ± 2	3.6 ± 1.0	11.9 ± 0.8	6.4 ± 0.5	2.4 ± 0.2

Values are mean ± SEM; n = 5 for each compound.

* ED_{95} calculated as μg/kg bis-cation of free base.

† Injection to maximum twitch suppression.

‡ Injection to recovery to 95% twitch height.

constructed in cumulative fashion using doses beginning with an approximate ED_{95} dose for neuromuscular block (NMB) and doubling the dose every 5 min up to approximately 50–100× the NMB ED_{95}. The vagus and sympathetic trunks were stimulated 2 min after each dose and the observed response was calculated as a percentage of the control response. The vagal ID_{50} values (doses that produced 50% inhibition of the response to vagus nerve stimulation) and the sympathetic ID_{25} values (doses that produced 25% inhibition of the response to sympathetic nerve stimulation) were determined from mean, log-probit dose-response curves.

A response suggestive of histamine release was sought after each single bolus dose of the compounds. The presence of a greater than 20% decrease in mean arterial pressure, a 20% increase in heart rate, as well as drug-induced contraction of the nictitating membrane were used as indicators suggestive of histamine release. The smallest dose resulting in observation of two of these indicators was considered the one causing the presumptive syndrome.

Plasma histamine concentrations were determined using a commercially available histamine enzyme immunoassay kit (Amac, Westbrook, ME). Five 3-ml arterial blood samples were obtained just before and 1, 2.5, 5, and 10 min after the bolus administration of 4,000 μg/kg cisatracurium or atracurium. Each sample was immediately placed in chilled polypropylene tubes containing 50 μl ethylenediaminetetraacetic acid and centrifuged within 5 min. The plasma was removed, kept chilled, and assayed immediately or stored at −80°C until assayed.

Two different batches of the isomers (mesylate salts and besylate salts) and atracurium besylate were used in these experiments. The doses reported represent the weight of the parent bis-cation. Atracurium and the isomers were dissolved in cold, 0.9% NaCl with *p*H level of 3 and prepared fresh daily. The optical and geometric designations and the corresponding Burroughs Wellcome numbers of the six isomers are as follows: S,Trans-S',Trans (34W89), S,Cis-S'Trans (35W89), S,Cis-S',Cis (36W89), R,Trans-R',Trans (49W89), R,Cis-R',Trans (50W89), and R,Cis-R',Cis (51W89, Cisatracurium). The commercially available preparation of vecuronium was used for experiments performed with that agent.

Results

Neuromuscular

Like atracurium, all six isomers produced dose-dependent inhibition of the evoked tibialis anterior twitch. The log-probit dose-response curves for atracurium and the six isomers were all parallel. The calculated (mean ± SE) NMB doses are summarized in table 1. The NMB ED_{95} values varied tenfold. Two "S-series" isomers were significantly less potent than atracurium. One was equipotent and the three "R-series" isomers were more potent than atracurium. All six isomers and atracurium were significantly less potent than vecuronium.

Also summarized in table 1 are the neuromuscular blocking effects observed for each agent at an approximate ED_{95} NMB dose. These data were obtained from

responses observed in individual cats (n = 5 for each agent). In each case, the magnitude of inhibition of the tibialis twitch ranged from 95% to 99%. The onset times for the six isomers and atracurium (fig. 1 and table 1) varied inversely with NMB potency. Similarly, the total durations of action of the isomers and atracurium (table 1) varied inversely with NMB potency (coefficient of correlation of best fit line = 0.94). With the exception of the relatively short duration of the S,Trans-S′,Trans isomer, the total durations of the other five isomers were not significantly different from atracurium or vecuronium. The 5–95% and 25–75% recovery times of the six isomers indicate that, like atracurium, all undergo relatively rapid spontaneous recovery.

The neuromuscular blocking effects of cisatracurium, atracurium, and vecuronium observed after the administration of 1× and 4× the ED_{95} NMB doses and continuous infusions of doses that maintained 95–99% neuromuscular block for at least 60 min are shown in figure 2. All three agents had similar onsets and total durations of action after the 1× or 4× the NMB ED_{95} doses. The recovery indexes for cisatracurium, observed after the bolus injections of the 1× and 4× ED_{95} NMB doses and after infusions were not significantly different from each other (table 2) and indicate that, like atracurium, recovery is independent of dose or duration of neuromuscular block. In contrast, the 5–

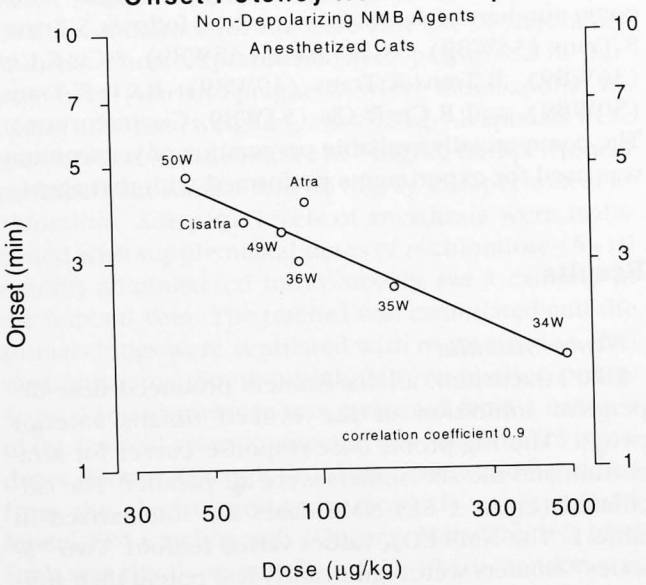

Fig. 1. The relationship between onset time (min) to 95–98% tibialis anterior twitch depression and the calculated ED_{95} NMB doses (μg/kg) in anesthetized cats. The log-onset time is the time from injection to peak effect. The data points represents the mean ± SEM, n = 5 for each agent. 50W = R,Cis-R′,Trans (50W89); Cisatra = cisatracurium (51W89); 49W = R,Trans-R′,Trans (49W89); Atra = atracurium; 36W = S,Cis-S′,Cis (36W89); 35W = S,Cis-S′,Trans (35W89); and 34W = S,Trans-S′,Trans (34W89).

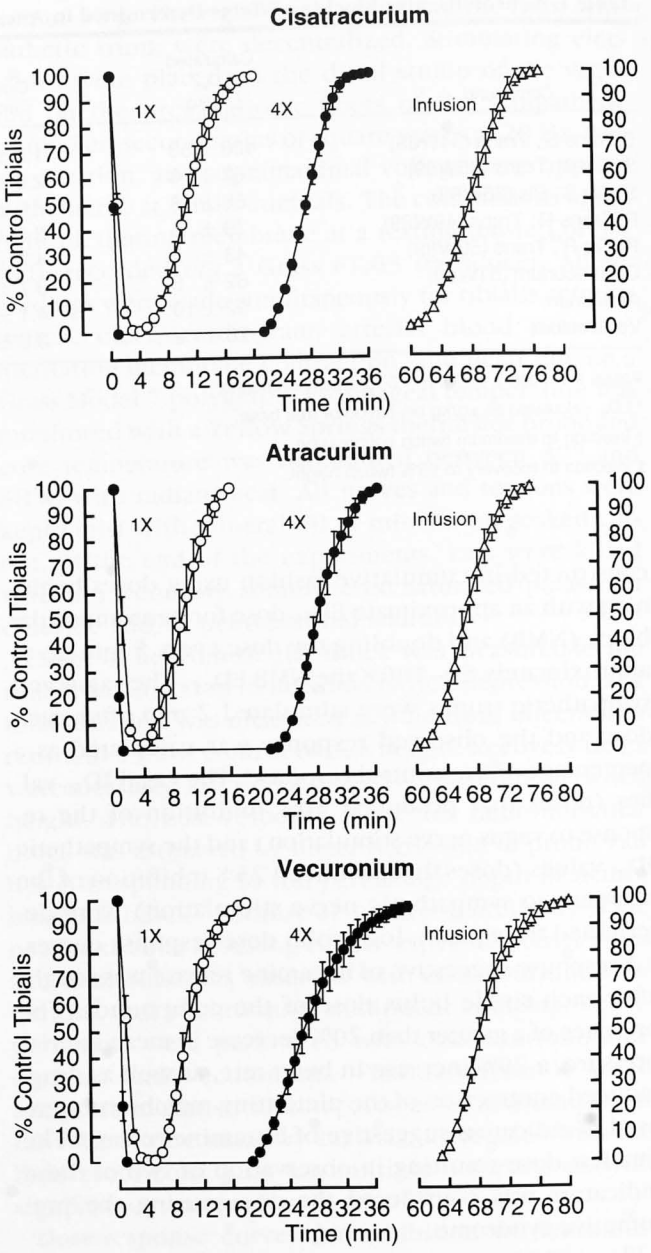

Fig. 2. Neuromuscular effects after approximate 1× ED_{95}, 4× ED_{95} doses, and infusions of cisatracurium (*top*), atracurium (*middle*), and vecuronium (*bottom*). Data points represent mean ± SEM (n = 5 for each agent). Doses as in table 2.

Table 2. Recovery Times Following 1× ED_{95}, 4× ED_{95}, and ED_{95-99} Infusion Doses of Cisatracurium, Atracurium, and Vecuronium in Anesthetized Cats

Compound	Dose (μg/kg)	Recovery Times (min) 5–95%	25–75%
Cisatracurium	1×: 67 ± 4	10.3 ± 0.7	4.4 ± 0.4
	4×: 250	9.3 ± 0.8	4.5 ± 0.4
	Infusion: 4.01 ± 0.16/min	10.8 ± 0.7	4.8 ± 0.4
Atracurium	1×: 92	7.3 ± 0.7	3.1 ± 0.3
	4×: 368	9.9 ± 1.1	4.7 ± 0.6
	Infusion: 5.02 ± 0.29/min	9.6 ± 1.2	3.9 ± 0.5
Vecuronium	1×: 21 ± 1	8.6 ± 1.0	3.5 ± 0.4
	4×: 96	17.4 ± 2.3	6.9 ± 1.0
	Infusion: 1.21 ± 0.08/min	10.9 ± 1.4	4.5 ± 0.6

Values are mean ± SEM; n = 5 for each agent.

95%, and 25–75% recovery indexes observed after the 4× ED_{95} NMB dose of vecuronium were significantly longer than the corresponding indexes observed after the 1× ED_{95} NMB dose and the infusions.

Antagonism with Neostigmine or Edrophonium

The administration of 50 μg/kg intravenous neostigmine or 500 μg/kg intravenous edrophonium at 85% block of the tibialis anterior twitch produced by cisatracurium after an approximate ED_{95} NMB dose, significantly decreased the 5–95% times (range 43–65%) and 25–95% times (range 70–93%). Similar effects with the anticholinesterases were observed with all of the other isomers.

Autonomic Nervous System

The relationships between the dose-response curves for neuromuscular block and inhibition of the responses to vagal and sympathetic nerve stimulations observed after large doses (530–5,300 μg/kg) of cisatracurium are shown in figure 3. The ratios of the dose that produced 50% inhibition of the response to vagal nerve stimulation (vagal ID_{50}) to the NMB ED_{95} neuromuscular blocking dose and the ratios of the dose that produced 25% inhibition of the response of the nictitating membrane to sympathetic nerve stimulation (sympathetic ID_{25}) to the NMB ED_{95}, observed after the administration of each of the six isomers, as well as atracurium, or vecuronium, are summarized in table 3. The vagal ID_{50}:NMB ED_{95} ratios varied 14-fold and the sympathetic ID_{25}:NMB_{95} varied 22-fold.

Histamine

Doses of the six isomers and atracurium that produced cardiovascular effects after rapid bolus injection are

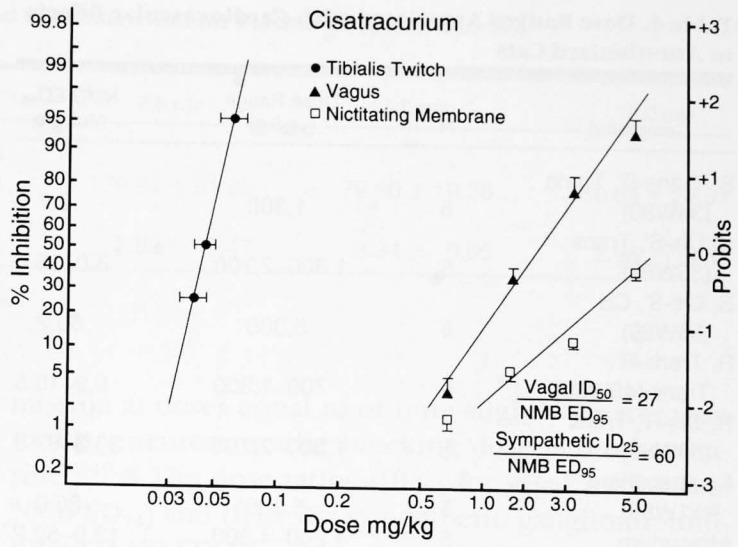

Fig. 3. Dose-response curves for inhibition of neuromuscular and parasympathetic and sympathetic autonomic responses by cisatracurium in anesthetized cats. Data points represent mean ± SEM (n = 5).

summarized in table 4. Atracurium and all of the isomers, except cisatracurium, produced cardiovascular effects (for typical response see fig. 4) over the same dose range in all the cats in each group. In these initial experiments, cisatracurium did not produce cardiovascular effects (for typical effects see fig. 4) at doses up to and including a dose equivalent to 85× the NMB ED_{95}. Plasma histamine concentrations were deter-

Table 3. Effects of Atracurium and Isomers on the Autonomic Nervous System in Anesthetized Cats

Compound	Neuromuscular ED_{95} (μg/kg)	Ratio 50% Vagus Inhibition *Versus* NMB ED_{95}	Ratio 25% Sympathetic Inhibition *Versus* NMB ED_{95}
S, Trans-S′, Trans (34W89)	488 ± 56	2	2.7
S, Cis-S′, Trans (35W89)	162 ± 6	14	21
S, Cis-S′, Cis (36W89)	88 ± 8	33	60
R, Trans-R′, Trans (49W89)	79 ± 6	22	60
R, Cis-R′, Trans (50W89)	43 ± 2	26	49
Cisatracurium (51W89)	62 ± 8	27	60
Atracurium	92 ± 10	17	34
Vecuronium	28 ± 2	19	57

Values are mean ± SEM; n = 5 for each agent.

Table 4. Dose Ranges Associated with Cardiovascular Effects in Anesthetized Cats

Compound	N	Dose Range (μg/kg)	NMB ED_{95} Multiple
S, Trans-S′, Trans (34W89)	5	1,300	2.7
S, Cis-S′, Trans (35W89)	5	1,300–2,700	8.0–16.6
S, Cis-S′, Cis (36W89)	5	5,300	60.2
R, Trans-R′, Trans (49W89)	5	700–1,300	8.9–16.5
R, Cis-R′, Trans (50W89)	5	1,300–2,700	30.2–62.8
Cisatracurium (51W89)	5	>5,300*	>80.0
Atracurium	5	1,200–4,800	13.0–52.2

* Four cats received 5,300 μg/kg, the fifth cat only received 2,700 μg/kg.

mined in a separate group of cats that received either cisatracurium or atracurium at intravenous bolus doses of 4,000 μg/kg. As summarized in table 5, cisatracurium had no significant effect on plasma histamine concentrations; whereas, plasma histamine concentrations rapidly increased approximately 100-fold within the first minute after the administration of atracurium. No cardiovascular effects were observed after the administration of 4,000 μg/kg intravenous cisatracurium, but were observed in all cats after 4,000 μg/kg intravenous atracurium.

Discussion

Neuromuscular

The results of this study indicate that all six isomers of atracurium had neuromuscular blocking activity. It is likely that all of the isomers contribute in a significant way to the NMB effects of atracurium, but possibly, because of the observed differences in potencies, onset times, and total durations, in an unequal way. None of the isomers produced muscle fasciculations or potentiation of twitch contraction, but all produced partial "tetanic fade" and "posttetanic potentiation" (data not presented) and were pharmacologically antagonized by the acetylcholinesterase inhibitors, neostigmine or edrophonium. Thus, the observed neuromuscular block had the characteristics of a nondepolarizing type of mechanism. The reason for the tenfold range of potencies is not known at this time, but it may be owing to a combination of enzymatic hydrolysis by plasma esterases in the cat and receptor affinity, and is most likely not owing to different rates of Hofmann elimination, the latter being a chemical reaction likely not influenced by stereochemical differences. The finding that the R-isomers were more potent than the corresponding S-isomers is in agreement with Stenlake *et al.* with the R and S isomer mixtures. The significant, inverse relationship between potency and onset time observed after the administration of equieffective neuromuscular blocking doses of the isomers and atracurium (fig. 1), support the hypothesis that nondepolarizing neuromuscular blocking agents of low potency have a more rapid onset of action than that seen with agents of high potency.[6–8] The significant, inverse relationship between duration and potency observed after the administration of approximate ED_{95} NMB blocking doses supports the suggestion that if a

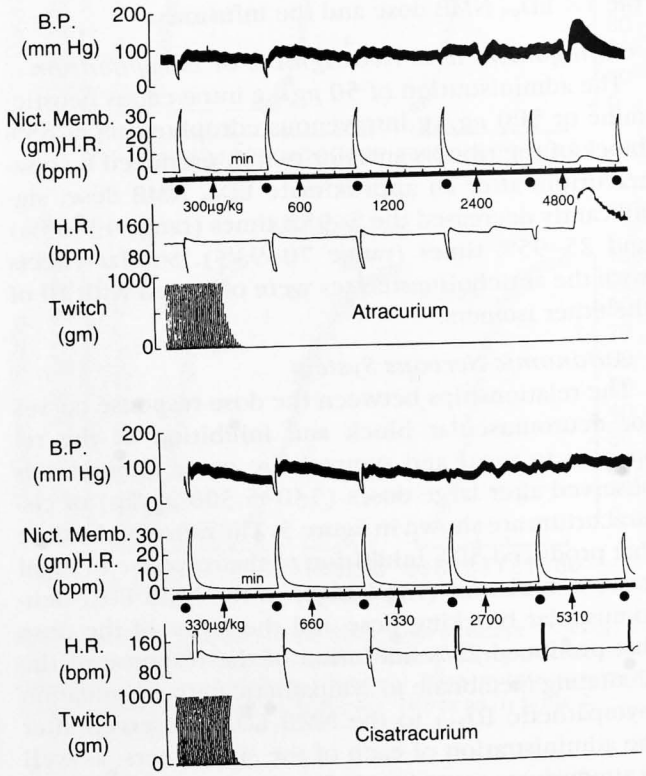

Fig. 4. Typical effects of bolus injections (at ↑) of supramaximal neuromuscular blocking doses of atracurium (*top*) and cisatracurium (*bottom*) on arterial blood pressure (BP), heart rate (HR), neuromuscular (twitch), and the sympathetic (nict memb) responses as well as parasympathetic responses (decreases of BP and HR) to nerve stimulation (at ●). Note cardiovascular effects (increase of HR and triphasic effect on BP) after 4,800 μg/kg atracurium.

Table 5. Effects of Intravenous Administration of Atracurium and Cisatracurium on Plasma Concentrations of Histamine in Anesthetized Cats

Drug	Control	1.0 min	2.5 min	5.0 min	10.0 min
Atracurium 4,000 μg/kg (43.5 × NMB ED_{95})	4.78 ± 0.99	438.44 ± 135.79	179.94 ± 51.66	79.60 ± 19.50	69.54 ± 22.91
Cisatracurium 4,000 μg/kg (64.5 × NMB ED_{95})	2.48 ± 0.47	3.76 ± 0.37	2.82 ± 0.47	3.34 ± 0.65	2.96 ± 0.31

Values are mean ± SEM (plasma histamine concentrations, nM); n = 5 for each agent.

nondepolarizing equivalent of succinylcholine is discovered, it is likely to be a neuromuscular blocking agent of low potency.[3,8]

The total durations ranged from approximately 8 to 14 min with most of the isomers having a total duration similar to that of atracurium. The S,Trans-S′,Trans isomer's total duration of 7.8 min ± 0.5 min is twice the total duration of an equieffective dose of succinylcholine (3.8 min ± 0.2 min) in our anesthetized cats. Tsui *et al.* reported that components of the Trans-Trans isomer groups may be hydrolyzed at different rates in human blood.[3] The differences in potency and duration observed in this study between the S,Trans-S′,Trans and R,Trans-R′,Trans isomers support his findings. Conversely, our results indicate that the S,Cis-S′,Trans and the R,Cis-R′,Trans isomers do not represent the proposed rapidly degraded components of the Cis-Trans isomeric group. It is likely that the other two isomers in the Cis-Trans isomeric group (R,Cis-S′,Trans and S,Cis-R′,Trans) have neuromuscular blocking profiles similar to the Cis-Trans isomers we tested; because, if hydrolysis occurs, it will occur at any one of the ester sites common to either the R,S, or meso isomers. The total duration of most of the isomers, especially the R-series, were very similar to both atracurium and vecuronium and, like atracurium and vecuronium, would be classified as intermediate-duration agents.

Autonomic

The effects of the isomers on the autonomic nervous system are typical of benzylisoquinolinium compounds. The only clinically available benzylisoquinolinium that will cause blockade of ganglionic transmission at doses equal to or only slightly greater than its ED_{95} neuromuscular blocking dose is d-tubocurarine.[9,10,#] The dose ratios ([ID_{50} for vagal inhibition/NMB ED_{95}] and [ID_{25} for sympathetic ganglionic inhibition/NMB ED_{95}]) in cats are useful because they represent ratios that gauge the relative likelihood of occurrence of autonomic effects in humans under anesthesia. With the exception of the S,trans-S′,trans isomer, all of the isomers had vagal ID_{50}/NMB ED_{95} values greater than 10, with even higher sympathetic ID_{25}/NMB ED_{95} ratios. The low ratios observed with the S,trans-S′,trans isomer are caused by its low NMB potency rather than an increased potency at autonomic receptors. The other five isomers, like atracurium, have a selective effect at the neuromuscular nicotinic receptor. These data are in agreement with many other comparisons in the cat of neuromuscular blocking properties *versus* autonomic effects that forecast a lack of cardiovascular effects in humans as a result of the autonomic effects of benzylisoquinolinium neuromuscular blockers.

Histamine

Histamine release is thought to be the principal mechanism by which the newer benzylisoquinolinium neuromuscular blocking agents, *e.g.,* atracurium and mivacurium, produce cardiovascular effects in humans.[**] In testing new drugs, investigators attempt to measure histamine release by several different methods, including histamine release from mast cell preparations, animal studies, and human studies. It is important to note that the amount of histamine in mast cells and the susceptibility to be released by chemical agents are both species and tissue dependent. We have chosen to study the cardiovascular effects of bolus intravenous injections of high doses of neuromuscular blocking agents in anesthetized cats as an initial index of histamine release because of our previous preclinical and clinical experiences with three benzylisoquinolinium

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neuromuscular blocking agents: atracurium, doxacurium, and mivacurium. Bolus intravenous administration of each of the five isomers of atracurium and atracurium itself produced decreases in arterial blood pressure, tachycardia in all of the 30 cats tested (n = 5 per compound), and in most cases, a small spontaneous contraction of the nictitating membrane. These responses were taken as indicative of the "histamine-release" syndrome. Cisatracurium, like vecuronium, did not produce this syndrome in any of the cats tested even though higher doses were administered (5,300 μg/kg, n = 4 and 2,600 μg/kg, n = 1). This finding was supported in a second study where it was observed that 4,000 μg/kg intravenous bolus injection of atracurium produced the typical histaminelike cardiovascular effects and increased the plasma histamine concentration more than a 100-fold, whereas, cisatracurium at an identical dose did not affect plasma histamine concentrations. Similar observations were observed in both anesthetized dogs (unpublished) and rhesus monkeys.†† Notably, in support of the findings with cisatracurium in cats, Lien *et al.* have reported that cisatracurium did not affect plasma histamine concentrations or produce important cardiovascular effects at doses up to and including eight times its human ED_{95} NMB dose in healthy patients undergoing elective surgical procedures.[11] To date, cisatracurium is the only benzylisoquinolinium neuromuscular blocking agent that does not produce cardiovascular effects or increase plasma histamine concentrations in experimental animals or humans at the doses tested.

Cisatracurium

These initial results identified cisatracurium, the R-R′ optical isomer of the *cis-cis* configuration, which represents about 15% of the atracurium mixture, as a neuromuscular blocking agent that was 1.5 times more potent than atracurium, had neuromuscular blocking effects and lack of autonomic effects very similar to that of atracurium, yet was devoid of the cardiovascular and histamine-releasing properties of atracurium. Additional neuromuscular studies were subsequently performed for comparisons to the standard intermediate-duration neuromuscular blocking agents, atracurium and vecuronium. The absence of significant differences in the 5–95% and 25–75% recovery times after two different bolus doses or a 1-h infusion indicated that cisatracurium, like atracurium and unlike vecuronium, did not have cumulative effects in anesthetized cats. A lack of cumulative effects and a consistent pattern of recovery independent of the size of the bolus doses or the length of infusions of cisatracurium was recently reported in human adults by Belmont *et al.*[12] and in children by Meretoja *et al.*[13] These investigators also reported that, as in the cat, cisatracurium was more potent than atracurium, had a duration of action similar to that of atracurium, and its neuromuscular blocking effect was antagonized by neostigmine. The only difference in the neuromuscular blocking effects noted in both humans and cats was the significantly slower onset time of cisatracurium in comparison with equipotent doses of atracurium. The most likely explanation for this observation is the greater difference in neuromuscular potency between cisatracurium and atracurium observed in humans (3×) and cats (1.5×). In summary, the current study has identified cisatracurium as nondepolarizing neuromuscular blocking agent with overall neuromuscular blocking effects very similar to that of atracurium. Unlike atracurium and five other available component isomers in the atracurium mixture, cisatracurium does not produce cardiovascular effects or affect plasma histamine concentrations after the administration of large bolus doses. The observed greater potency and intermediate duration of action, consistent pattern of recovery and lack of cumulative effects, pharmacologic antagonism by anticholinesterases, as well as a lack of autonomic, cardiovascular and histaminelike effects have been confirmed in human studies.[11–13,‡‡] The data indicate that cisatracurium represents an improved atracurium.

The authors thank Lois J. Cooper, for technical assistance with all animal experiments presented in this study; Dr. Eric Yung Sheng Wang, for the plasma histamine assays; and Gary L. LaMunion, Patricia F. Burns, and Judy A. McDuffie, for their assistance in data collection and manuscript preparation.

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