Preclinical pharmacology of cisatracurium besylate

William B. Wastila, Robert B. Maehr, Gary L. LaMunion, Matthew R. Belmont and John J. Savarese*

Atracurium is a mixture of 10 isomers. Six of the 10 isomers have been prepared and evaluated for neuromuscular, autonomic and cardiovascular effects in various anaesthetized animal species, including rats, cats, dogs and Rhesus monkeys. All of the isomers exhibited neuromuscular-blocking activity with a 10-fold range of potency, and with the exception of cisatracurium (the purified R-*cis*,R′-*cis* isomer), produced autonomic and cardiovascular effects at doses similar to those of atracurium. Cisatracurium was found to be more potent than atracurium in all of the preclinical studies and, unlike atracurium and all the other isomers, bolus injections of high multiples of the 95% effective neuromuscular-blocking dose did not produce histamine-like cardiovascular effects or increase plasma histamine concentrations. In preclinical studies it was concluded that cisatracurium represents a significant improvement over atracurium.

Glaxo Wellcome Inc., Research Triangle Park, North Carolina, USA, and *Department of Anesthesiology, New York Hospital–Cornell Medical Center, 525 East 68th Street, New York, NY 10021, USA

Corresponding author: William B, Wastila, Glaxo Wellcome, 3030 Cornwallis Road, Research Triangle Park, NC 27709, USA

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Abbreviations

ED_{95}	dose that produces 95% of the maximum response
ID_{50}	dose that produces 50% inhibition of the response

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Introduction

Atracurium, like vecuronium, is a non-depolarizing, intermediate-duration neuromuscular-blocking agent [1,2] and became available for human use as an adjunct to general anaesthesia in the United Kingdom and United States in 1982 and 1983, respectively. Atracurium was designed to undergo spontaneous degradation to inactive breakdown products at physiological pH and temperature by a process called Hofmann elimination [3]. This unique Hofmann elimination feature is the reason for its clinical advantages (lack of cumulative properties, predictable recovery, organ-independent elimination). However, like other benzylisoquinolinium (curare-like) neuromuscular-blocking agents, atracurium has the disadvantage of producing histamine-mediated cardiovascular side effects [4,5] at higher doses given during clinical practice.

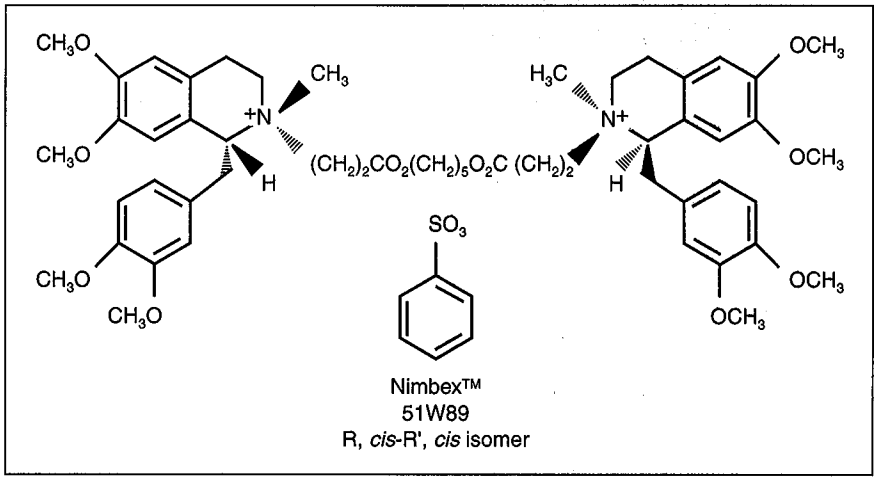
Atracurium has four chiral centres at C(1) and N(2) in the two tetrahydropapaverine units (Fig. 1). Because of molecular symmetry, the 16 theoretically possible isomers are reduced to 10. Since the synthesis of atracurium, we have attempted to isolate and evaluate each of the 10 isomers found in the atracurium mixture. To this end, chemists at our Dartford Chemical Development Laboratories, G.L. Turner and D.A. Hill, have prepared six of the isomers in quantities sufficient for testing in experimental animals. For simplicity, the optical and geometrical configuration of the six isomers are as follows: S-*trans*,S′-*trans*; S-*cis*, S′-*trans*; S-*cis*,S′-*cis*; R-*trans*,R′-*trans*; R-*cis*,R′-*trans*; and R-*cis*,R′-*cis*. The corresponding Glaxo Wellcome registry numbers are 34W89, 35W89, 36W89, 49W89, 50W89 and 51W89. In the studies reported below, atracurium and the six available isomers were initially evaluated for neuromuscular-blocking activity, autonomic effects and histamine-like cardiovascular effects in anaesthetized cats. Additional comparative neuromuscular experiments were performed with the intermediate-duration neuromuscular- blocking agents vecuronium and rocuronium. Cardiovascular studies were also performed in anaesthetized beagle dogs and Rhesus monkeys.

Cisatracurium

Several studies, including some of the results reported here, have been published previously [6–12]. These reports have referred to cisatracurium as 51W89, the R-*cis*,R′-*cis* isomer, cisatracurium besylate or Nimbex. The stereochemical structure of cisatracurium is illustrated in Fig. 1. R designates the absolute stereochemistry of the tetrahydropapaverine rings and *cis* represents the relative geometry of the bulky dimethoxy and 2-alkyester groups at C(1) and N(2), respectively. Like atracurium, cisatracurium is formulated as the

Figure 1

Structure of cisatracurium. The conformation of substituents at the four chiral centres is shown by the three-dimensional bonds.



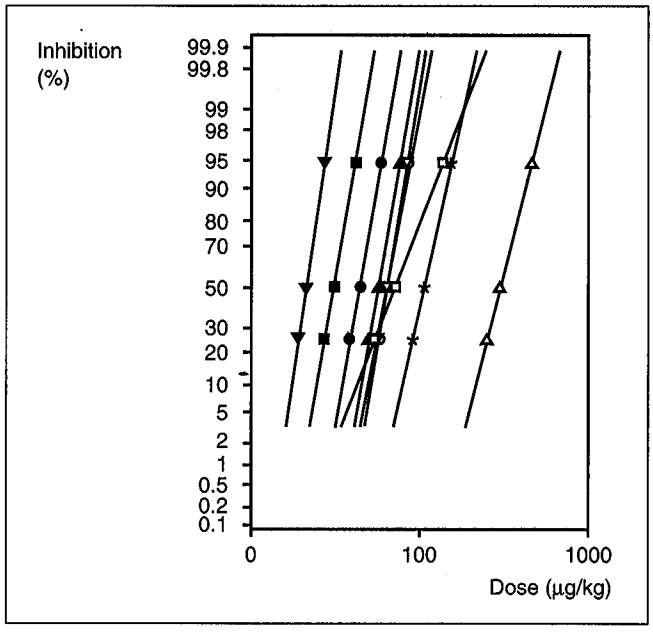
besylate salt. However, cisatracurium represents 15% of the marketed atracurium mixture by weight but more than 50% in terms of potency or neuromuscular-blocking activity. Doses of older neuromuscular-blocking drugs are traditionally reported in terms of the salt, whereas newer drugs are described in terms of the free base, usually a bis-cation. In order to allow valid comparisons of potency and other features, doses of all neuromuscular-blocking agents reported here have been recalculated as the weight of their bis-cations or free bases.

Neuromuscular effects

The neuromuscular dose–response curves for inhibition of the tibialis anterior twitch produced by atracurium, the six isomers and the steroidal blocking agents vecuronium and rocuronium in α-chloralose-anaesthetized cats are shown in Fig. 2. With the exception of the dose–response curve for rocuronium, the curves are parallel. In general, atracurium, the six isomers and rocuronium were less potent than vecuronium. The doses calculated to produce 95% of the maximum effect (ED_{95}) indicated that the potency of the isomers varied 10-fold (ED_{95} 43 ± 2–488 ± 56 μg/kg). Two of the isomers, S-*trans*, S′-*trans* (ED_{95} 488 ± 86 μg/kg) and S-*cis*, S′-*trans* (ED_{95} 162 ± 6 μg/kg) were less potent than atracurium (ED_{95} 92 ± 10 μg/kg). The S-*cis*, S′-*cis* isomer (ED_{95} 88 ± 8 μg/kg) was similar in potency to atracurium. Cisatracurium (ED_{95} 62 ± 8 μg/kg) and two other isomers (R-*trans*, R′-*trans*, ED_{95} 79 ± 6 μg/kg; R-*cis*, R′-*trans*, ED_{95} 43 ± 2 μg/kg) were more potent than atracurium. All of the R series isomers were more potent than the corresponding S series. The increased neuromuscular potency of cisatracurium compared to atracurium in the cat was also observed in pentobarbital-anaesthetized rats and dogs, N_2O/O_2/halothane-anaesthetized Rhesus monkeys and, subsequently, in humans under N_2O/opioid/barbiturate anaesthesia (Table 1).

The time to peak effect in cats following an approximate neuromuscular-blocking ED_{95} (actual responses ranged from 95 to 99% inhibition of the tibialis twitch) of atracurium and

Figure 2



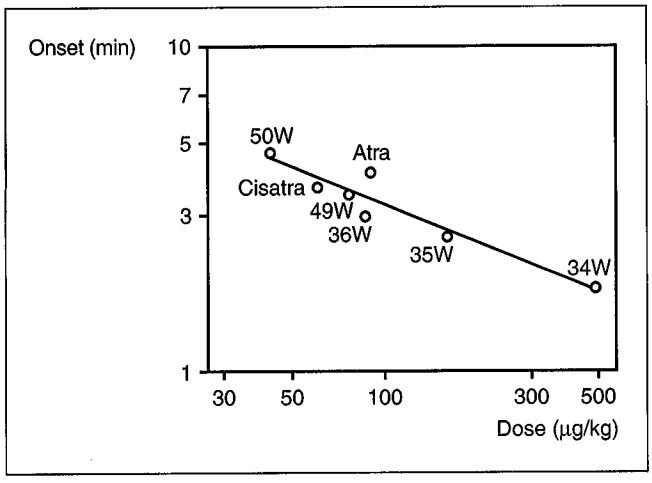
Log-probit neuromuscular dose–response curves for inhibition of the tibialis anterior twitch in α-chloralose anaesthetized cats; n = 5 for each agent. ▼, Vecuronium; ■, 50W89; ●, cisatracurium; ▲, 49W89; O, 38W89; ▽, atracurium; □, rocuronium; *, 35W89; △, 34W89.

Table 1. Doses that produced 95% neuromuscular blockade (ED_{95}).

	Cisatracurium (μg/kg)	Atracurium (μg/kg)
Rat	437 ± 36	993 ± 133
Cat	62 ± 8	92 ± 10
Dog	49 ± 1	59 ± 4
Rhesus monkey	78–83	150
Human	50	170

Values are expressed as means ± SEM (unless n < 3).

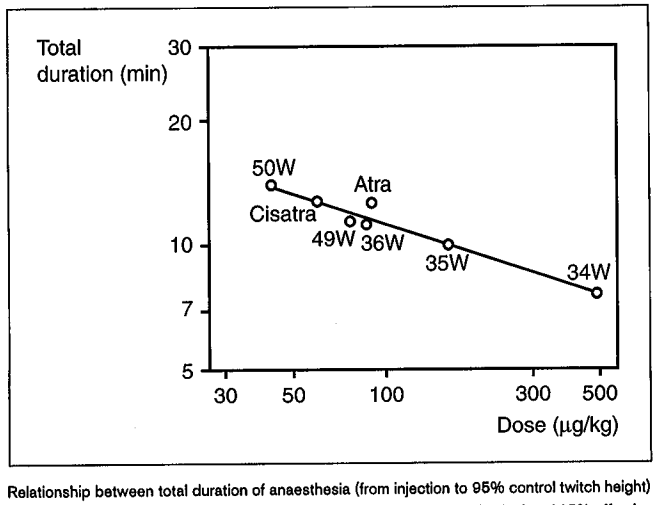
Figure 3



Relationship between onset time (from injection to peak effect) to 95–98% tibialis anterior twitch depression and calculated 95% effective neuromuscular-blocking doses (ED_{95}) in anaesthetized cats. Data points represent the means from five cats for each agent. Correlation coefficient, 0.95. Isomers: 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); 34W, S-*trans*,S'-*trans* (34W89).

the six isomers ranged from 1.8 ± 0.1 to 4.7 ± 0.3 min. The onset times for cisatracurium (3.7 ± 0.1 min) and atracurium (4.1 ± 0.2 min) were not significantly different ($P < 0.05$). The onset times for atracurium and the six isomers varied inversely with neuromuscular-blocking potency (Fig. 3). This observation was highly significant, with a coefficient of correlation of the best fit for log onset/log potency of 0.95. The total duration of action (time from injection to return to 95% of control twitch height) for atracurium and the isomers at approximate neuromuscular-blocking ED_{95} ranged from 7.8 ± 0.5 to 14.0 ± 0.9 min (Fig. 4). The total duration of neuromuscular block also varied inversely with potency, with a coefficient of correlation of best fit of 0.94.

Figure 4



Relationship between total duration of anaesthesia (from injection to 95% control twitch height) at doses that produced 95–98% tibialis anterior twitch depression and calculated 95% effective neuromuscular-blocking doses in anaesthetized cats. Data points represent the means from five cats for each agent. Correlation coefficient, 0.94. Isomers: 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); 34W, S-*trans*, S'-*trans* (34W89).

The results summarized in Table 2 indicate that the total duration of neuromuscular block observed after a neuromuscular-blocking ED_{95} of cisatracurium was identical to that observed after atracurium and very similar to that of the steroidal intermediate-duration agents vecuronium and rocuronium. Thus cisatracurium can be classified as an intermediate-duration neuromuscular-blocking agent.

Table 3 summarizes the 5–95% recovery times observed after the administration of cisatracurium at one and four times the neuromuscular-blocking ED_{95} and after infusions that maintained a 95–99% neuromuscular block for at least 60 min. There were no significant differences in recovery times following these three doses, which indicated that cisatracurium, like atracurium, and unlike vecuronium and rocuronium, did not have cumulative effects in anaesthetized cats.

Table 2. Neuromuscular-blocking profiles in anaesthetized cats.

Compound	ED_{95} (μg/kg)	Onset (min)	Total duration (min)
Cisatracurium	62 ± 8	3.7 ± 0.1	12.7 ± 0.9
Atracurium	92 ± 10	4.1 ± 0.2	12.7 ± 1.4
Vecuronium	28 ± 2	3.6 ± 0.1	11.9 ± 0.8
Rocuronium	141 ± 2	21.8 ± 0.1	9.7 ± 1.2

Values are expressed as means ± SEM. ED_{95}, dose that produced 95% of the maximum effect calculated as μg/kg of mono- or bis-cation free base. All these agents are quaternary, but some have two N^+ moieties and some have only one N^+.

Table 3. Recovery times following the dose that produced 95% of the maximum effect (ED_{95}), four times the ED_{95} and ED_{95-99} infusion doses of cisatracurium, atracurium and rocuronium in anaesthetized cats.

	Dose		Recovery times (min)
Compound	(×ED_{95})	(μg/kg)	5 → 95%
Cisatracurium	1	67 ± 4	10.3 ± 0.7
	4	250	9.3 ± 0.8
	Infusion	4.01 ± 0.16/min	10.8 ± 0.7
Atracurium	1	92	7.3 ± 0.7
	4	368	9.9 ± 1.1
	Infusion	5.02 ± 0.29/min	9.6 ± 1.2
Vecuronium	1	21 ± 1	8.6 ± 1.0
	4	96	17.4 ± 2.3
	Infusion	1.21 ± 0.08/min	10.9 ± 1.4
Rocuronium	1	140	5.2 ± 0.8
	4	560	8.7 ± 0.9
	Infusion	12.9 ± 2.0/min	6.7 ± 0.7

Values are expressed as means ± SEM (n = 5 for each agent). ED_{95} values were determined in different experiments, and therefore there are minor differences between values shown here and some shown elsewhere. Multiples of the ED_{95} are approximate; the actual doses given are reported precisely and were chosen for ease of administration.

Autonomic and cardiovascular effects

The selectivity of cisatracurium for the neuromuscular junction was demonstrated in α-chloralose-anaesthetized cats. Figure 5 shows that there is a wide separation between the neuromuscular-blocking ED_{95} and doses that affect the autonomic nervous system. Similar studies in anaesthetized cats performed in our laboratory with other clinically available non-depolarizing neuromuscular-blocking agents (Table 4) showed good agreement with previously reported values [13–18]; these results indicate that cisatracurium, like atracurium, vecuronium, mivacurium and doxacurium, will be devoid of vagolytic effects at therapeutic doses.

In anaesthetized cats, bolus injections of atracurium over a dose range of 1.5–5.0 mg/kg produce histamine-like cardiovascular effects [6]. Like atracurium, rapid bolus administration of all the isomers, with the exception of cisatracurium, over a dose range of 0.7–5.3 mg/kg produced transient decreases in arterial blood pressure and tachycardia in all of the cats tested (n = 5 for each agent). No histamine-like cardiovascular effects were observed in anaesthetized cats after the bolus administration of cisatracurium at doses as high as 5.3 mg/kg (85 times the cat neuromuscular-blocking ED_{95} and 100 times the human neuromuscular-blocking ED_{95}, respectively).

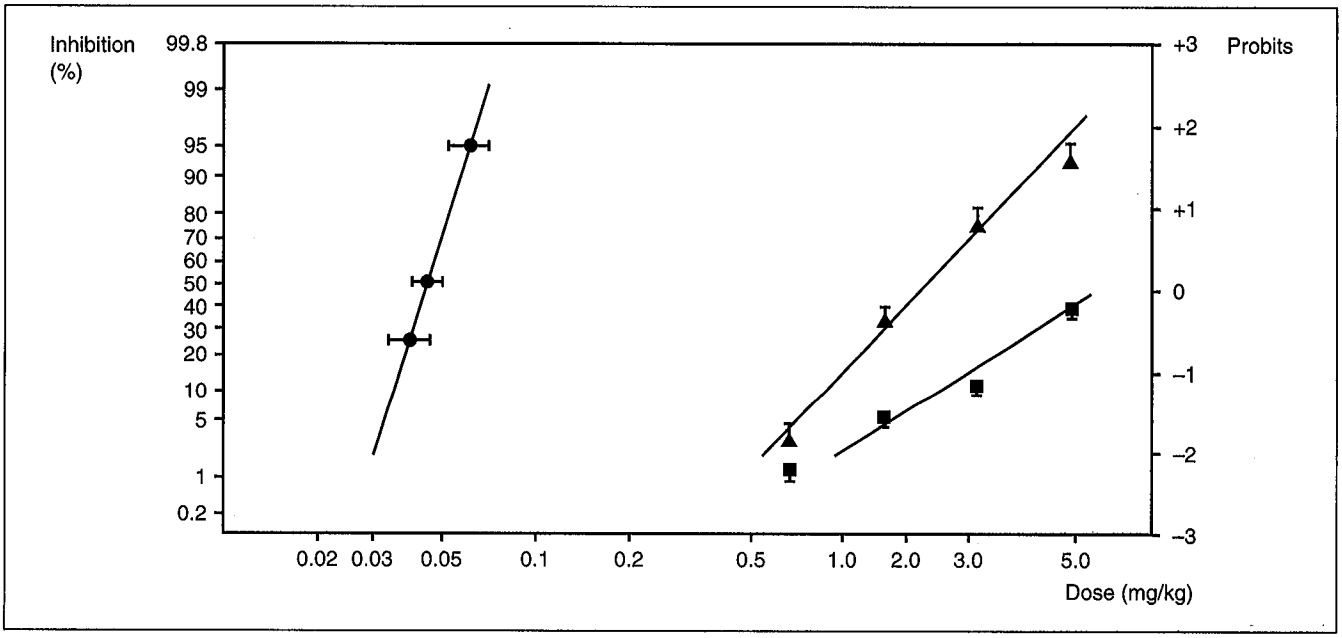
We have also examined the effects of bolus administration of a high dose of cisatracurium on plasma histamine concentrations in anaesthetized cats. Figure 6a shows the effects of a bolus dose of each agent (4.0 mg/kg; n = 5). Arterial blood samples taken immediately before and 1, 2.5, 5 and 10 min after drug administration showed that atracurium produced a 100-fold increase in the plasma histamine concentration while cisatracurium had no significant effect. A similar experiment (Fig. 6b) with atracurium administered 5 min after cisatracurium produced similar results. A decrease in arterial blood pressure and tachycardia was observed in all 10 atracurium-treated cats. No effects on arterial blood pressure or heart rate were observed in the 10 cisatracurium-treated cats.

The cardiovascular effects of cisatracurium and atracurium were also evaluated in anaesthetized beagle dogs (Fig. 7). Atracurium produced dose-dependent decreases in arterial blood pressure (15–55%) and heart rate (12–25%) over a dose range of 296 to 1184 μg/kg (equivalent to only 1.6–6.6 times the human neuromuscular-blocking ED_{95}). These large, precipitous, transient decreases in arterial blood pressure suggest

Table 4. Ratio of the dose that produces 50% inhibition of the heart rate response to vagus nerve stimulation to the dose that produces 95% effective neuromuscular blockade.

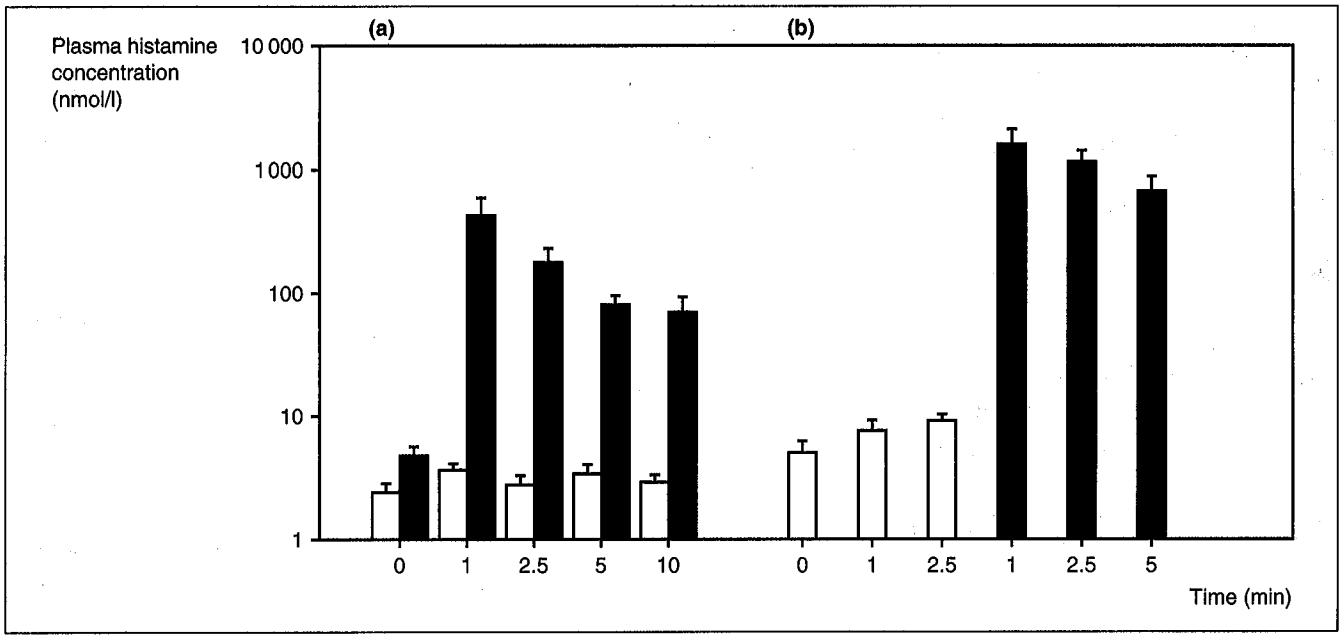
Tubocurarine	<1
Pancuronium	7
Rocuronium	7
Atracurium	17
Vecuronium	19
Cisatracurium	27
Mivacurium	55
Doxacurium	>100

Figure 5



Log-probit dose–response curves for inhibition of neuromuscular (tibialis anterior twitch, ●), parasympathetic (vagus, ▲) and sympathetic (nictitating membrane, ■) responses in anaesthetized cats (n = 5) by intravenous bolus cisatracurium. All measurements were made in the same cats. Data points are means ± SEM. The ratio of the dose that produced 50% inhibition (ID_{50}) of the heart rate response to vagus nerve stimulation to the 95% effective neuromuscular-blocking dose (ED_{95}) was 27; the sympathetic ID_{25} to ED_{95} ratio was 60.

Figure 6



Plasma histamine concentrations after a bolus dose (4.0 mg/kg, intravenously) of (a) either cisatracurium (n = 5) or atracurium (n = 5) and (b) cisatracurium followed by atracurium 5 min later in the same cats (n = 5). The histamine concentrations were measured in arterial blood samples taken immediately before and 1, 2.5, 5 and 10 min after the dose.

a release of endogenous histamine and can, in fact, be markedly attenuated by pretreatment with H_1 and H_2 histamine antagonists (W.B. Wastila, unpublished data, 1994). In contrast to atracurium, cisatracurium at up to 332 μg/kg (6.6 times the human neuromuscular-blocking ED_{95}) had no or minimal (<10%) effects on mean arterial blood pressure and heart rate. Higher doses (up to 1330 μg/kg, 26 times the human neuromuscular ED_{95}) produced slightly larger decreases in blood pressure (<20%) and heart rate (<10%). These effects observed with high doses of cisatracurium are most likely due to transient ganglionic inhibition. With this agent, there were no large, sudden decreases in arterial blood pressure at onset that might suggest a release of histamine.

Additional evidence that cisatracuriuim has no cardiovascular or histamine-like effects was obtained in Rhesus monkeys anaesthetized with N_2O/O_2/halothane (n = 4). Table 5 summarizes the peak effects on mean arterial blood pressure and heart rate after the bolus administration of cisatracurium over a dose range of 42–1328 μg/kg (equivalent to 0.8–26 times the human neuromuscular-blocking ED_{95}). Cisatracurium had no significant effects on these cardiovascular parameters. No facial flushing or cardiovascular effects that might suggest a release of endogenous histamine were observed.

Conclusions

The results reported in these studies indicated that all of the available isomers of atracurium have neuromuscular-blocking activity. Further details on the pharmacological profile of cisatracurium and the isomers of atracurium are reported elsewhere [19]. The results obtained in anaesthetized cats indicated that all three of the R series isomers (R-*trans*,R'-*trans*, R-*cis*,R'-*trans* and cisatracurium) were equipotent to or more potent than atracurium. The increased potency of cisatracurium compared to atracurium was confirmed in additional studies in rats, dogs, Rhesus monkeys and humans. These same three isomers had neuromuscular-blocking profiles similar to those of atracurium and had higher autonomic : neuromuscular ratios than atracurium.

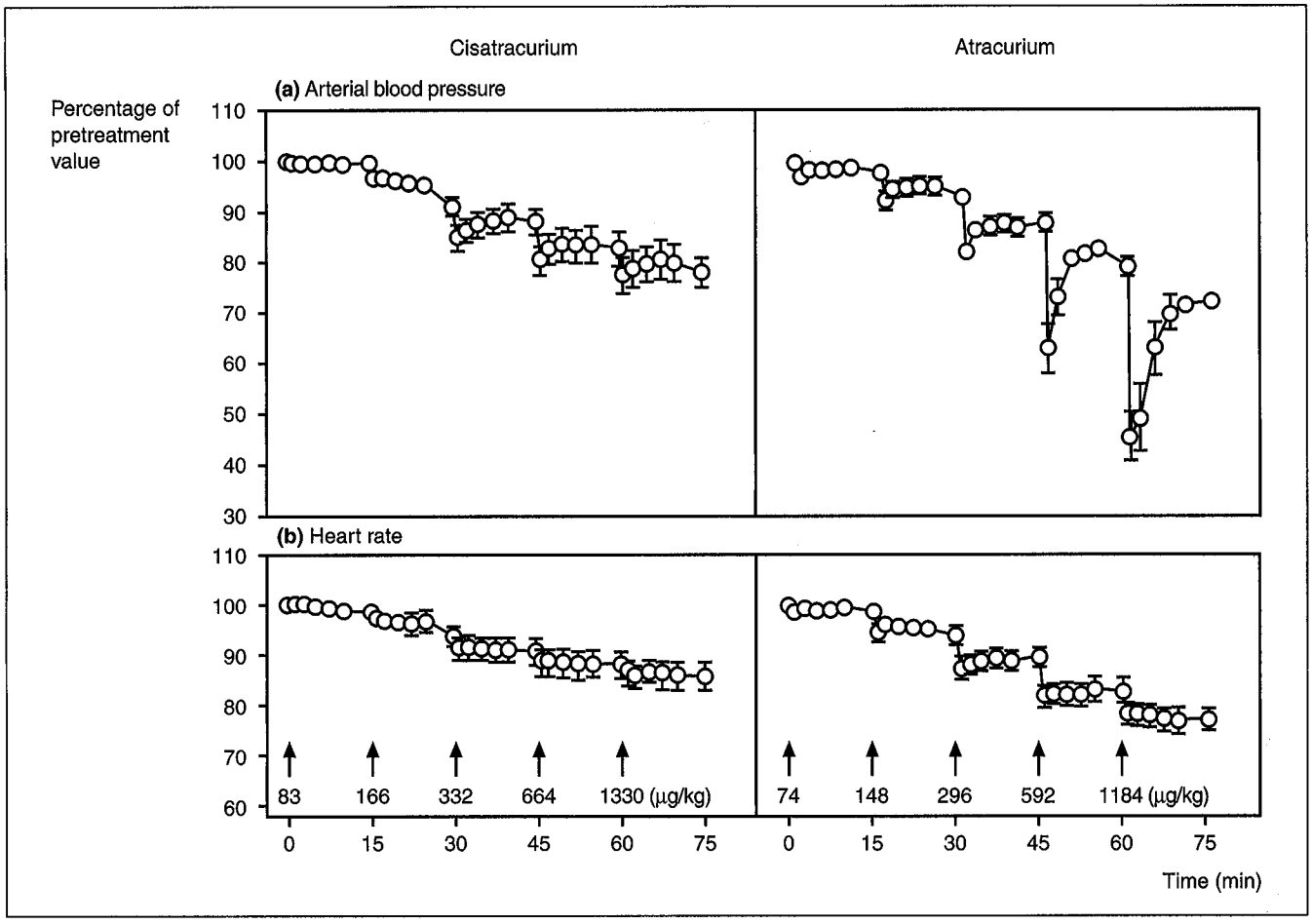
All the studies in various anaesthetized animal species have confirmed that cisatracurium is a non-depolarizing neuromuscular-blocking agent with an overall time profile similar to that of atracurium. Cisatracurium retains the important neuromuscular-blocking features of atracurium; it has an intermediate duration of action, a consistent pattern of recovery and is devoid of cumulative effects.

Table 5. Peak neuromuscular and cardiovascular effects of cisatracurium in anesthetized Rhesus monkeys (n = 4).

Dose (μg/kg)	Neuromuscular block (%)	Mean arterial blood pressure (% control)	Heart rate (% control)
42	43 ± 13	99 ± 1	98 ± 1
83	96 ± 2	102 ± 1	100 ± 2
166	100	102 ± 1	101 ± 1
322	100	100 ± 1	103 ± 1
664	100	98 ± 3	105 ± 1
1328	100	95 ± 6	103 ± 3

All values are mean ± SEM.

Figure 7



(a) Mean arterial blood pressure and (b) heart rate following bolus intravenous injections of cisatracurium or atracurium at 15-min intervals (↑; doses indicated) in beagle dogs anaesthetized with pentobarbitone. Values are expressed as mean ± SEM (n = 5) percentages of pretreatment control values (mean arterial pressure 126 ± 5 and 127 ± 7 mmHg, heart rate 147 ± 5 and 151 ± 7 beats/min, for cisatracurium and atracurium, respectively). The dose range for cisatracurium was equivalent to 6.6–26 times the human 95% effective neuromuscular-blocking dose (ED_{95}) compared with atracurium at only 1.6–6.6 times the ED_{95}. The final measurements (min 75) showed a mean arterial pressure of 98 ± 5 and 91 ± 5 mmHg and heart rate of 126 ± 3 and 117 ± 5 beats/min for cisatracurium and atracurium, respectively.

The principal distinguishing feature of cisatracurium is that it does not produce dose-related histamine-like cardiovascular effects or increase the plasma histamine concentration. Cisatracurium was the only isomer that did not produce histamine-like responses or affect plasma histamine concentrations after bolus administrations of high doses in cats. Doses of cisatracurium equivalent to >25 times the human neuromuscular-blocking ED_{95} did not produce histamine-like cardiovascular effects in anaesthetized dogs and Rhesus monkeys. Since the onset of neuromuscular block is independent of the dose, these results suggest that large doses of cisatracurium could be used to decrease the time to onset of neuromuscular block without the histamine-induced hypotension and facial flushing associated with high doses of atracurium.

On the basis of these preclinical studies, we conclude that cisatracurium provides significant improvements over atracurium. As cisatracurium combines the consistent recovery profile of atracurium with cardiovascular stability over a wide range of doses, it may also have a significant advantage over other available non-depolarizing neuromuscular-blocking agents. These results are of sufficient interest to warrant further development of cisatracurium as a therapeutic agent.

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