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A Comparison of the Neuromuscular Blocking and Autonomic Effects of Two New Short-acting Muscle Relaxants with Those of Succinylcholine in the Anesthetized Cat and Pig

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The actions of two new steroidal nondepolarizing neuromuscular blocking agents, structurally related to vecuronium, have been compared with those of succinylcholine in anesthetized cats and pigs. Both new compounds (Org 7617 and Org 9616) exhibited properties typical of nondepolarizing relaxants in each species. Org 9616 was one-fifth (ED_{50} cat tibialis 154 $\mu g \cdot kg^{-1}$) and Org 7617 was one-tenth (ED_{50} cat tibialis 287 $\mu g \cdot kg^{-1}$) as potent as vecuronium as a neuromuscular blocking drug. Both compounds produced rapidly developing muscle relaxation in cats that, like that of succinylcholine, was transient in time course (onset/duration of action—tibialis anterior muscle: Org 7617 1.6/3.9 min; Org 9616 1.5/4.3 min; succinylcholine 1.7/5.7 min). In pigs that were used as a predictor of duration of action in humans, both Org 7617 and Org 9616 also produced short-lived neuromuscular blockade. The neuromuscular blocks produced by Org 7617 and Org 9616 were readily reversed by neostigmine. Both compounds blocked the heart rate responses to vagal stimulation at doses higher than those required to produce neuromuscular block. The vagal:neuromuscular blocking ratio for Org 7617 was 10, and for Org 9616 was 17. These compare to approximate published values for vecuronium, atracurium, and pancuronium of 60, 25, and 3, respectively. Ganglion block was only seen at 30–60 times the neuromuscular blocking doses. Both compounds produced a decrease in arterial blood pressure. This was more pronounced with Org 7617. In addition, Org 9616 produced a slight increase in heart rate. The compounds represent examples of nondepolarizing drugs of moderate potency, having relatively minor autonomic and cardiovascular actions, but having an onset and a duration of action comparable to that of succinylcholine. (Key words: Autonomic nervous system. Neuromuscular relaxants, nondepolarizing: Org 7617; Org 9616; succinylcholine; vecuronium analogues.)

SINCE ITS INTRODUCTION into clinical practice in 1951–52, succinylcholine has remained the muscle relaxant of choice for procedures requiring only a brief period of relaxation.[1,2] However, because succinylcholine possesses several unwanted side effects, many attempts have been made to provide a nondepolarizing agent with a time course profile similar to that of succinylcholine. Thus far, all of these attempts have been frustrated either by the compounds exhibiting unwanted cardiovascular side effects in animals or by the inability to confirm in humans the short time course profile seen in experimental animals. Compounds in this class include gamma-oxalolaudonium,[3] Org NB68 (dacuronium),[4] fazadinium,[5] Org 6368,[6] chandonium,[7] and RGH-4201.[8]

In the early 1980s, two new relaxants, vecuronium and atracurium, were introduced. Both compounds possess durations of action shorter than those of the commonly used nondepolarizing relaxants, but their overall onset and duration remain longer than that of succinylcholine.[9,10] The advantages of these two compounds include their medium-length duration of action, their lack of cardiovascular side effects, and their low dependence on the kidney for their elimination. We have now examined the effects of two butyryl analogues of vecuronium, Org 7617 and Org 9616 (fig. 1). Org 7617 is the 16N-allyl, 17β-butyryl analogue of vecuronium, while Org 9616 differs from vecuronium only in possessing a 17α-butyryl group. These new compounds have been tested in anesthetized cats that have been used primarily to predict the neuromuscular blocking potency and onset time, and the cardiovascular and autonomic side effects, of the compounds; and, in anesthetized pigs, to assess the time course of action of the compounds.

Materials and Methods

All experiments were carried out under the regulations of the United Kingdom Cruelty to Animals Act 1876.

Anesthetized Cat Experiments

Experiments were carried out on cats of either sex anesthetized with a mixture of α-chloralose 80 $mg \cdot kg^{-1}$ and pentobarbital sodium 5 $mg \cdot kg^{-1}$ injected intraperitoneally. A right hind limb was immobilized and responses of the tibialis anterior and soleus muscles to single shock

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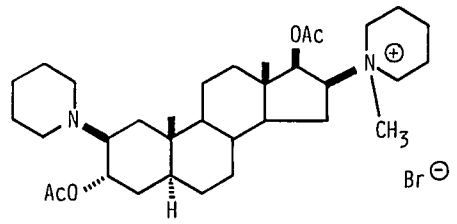
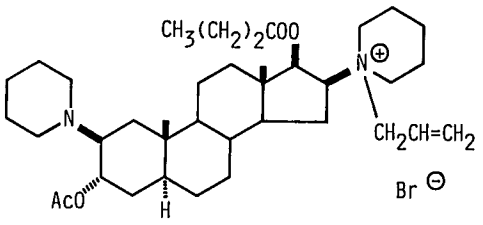
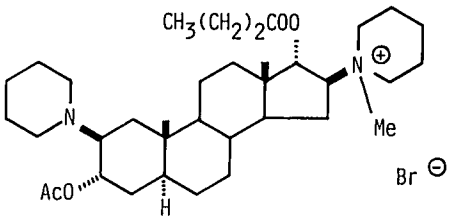


Vecuronium



Org 7617



Org 9616

FIG. 1. Chemical structure of vecuronium 1-[(2β,3α,5α,-16β,17β)-3,bis(acetyloxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methyl piperidinium bromide. Org. 7617 1-[(2β,3α,5α,16β,17β)-3-Acetyloxy-17-(1-oxobutoxy)-2-(1-piperidinyl)-androstan-16-yl]-1)-(2-propenyl) piperidinium bromide and Org 9616 1-[(2β,3α,5α,-16β,17α)-3-Acetyloxy-17-(1-oxobutoxy)-2-(1-piperidinyl)-androstan-16-yl]-1-methylpiperidinium bromide.

stimulation of the sciatic nerve were recorded. The sciatic nerve was stimulated at a rate of 0.1 Hz using rectangular pulses of 0.2 msec duration and of a strength greater than that required to produce a maximal twitch. Contractions of the nictitating membrane were produced in response to preganglionic stimulation of the cervical sympathetic nerve with 10-s duration trains at a frequency of 5 Hz and of strength sufficient to produce maximal contractions of the nictitating membrane. Arterial blood pressure was recorded from the carotid artery using a Statham PC45 pressure transducer. The blood pressure pulse triggered a cardiotachograph to display the heart rate. Both vagus nerves were ligated and, at 100-s intervals, the right vagus nerve was stimulated with 10-s trains at a frequency of 2–5 Hz and with pulses of 0.5 msec duration and of strength greater than that required to produce a maximal reduction in heart rate. Contractile responses of muscles were monitored by Grass FTO3C and FT10C force displacement transducers. All responses were displayed on a Grass model 5 ink writing oscillograph.

Experiments in Anesthetized Pigs

Domestic pigs (Landrace-Welsh cross) of either sex (10.4–15.1 kg) were administered a tranquillizing dose (approximately 2 $mg \cdot kg^{-1}$) of azaperone about 20 min before the induction of anesthesia with 3–4% halothane in oxygen. Following induction, anesthesia was maintained with α-chloralose 200 $mg \cdot kg^{-1}$ dissolved in polyethylene glycol 300 given slowly into the jugular vein. Approximately 1 h later, anesthesia was supplemented with additional chloralose given by a slow iv infusion (33 $mg \cdot kg^{-1} \cdot h^{-1}$) which was continued throughout the investigation. The lungs were mechanically ventilated with room air *via* a tracheal cannula at a rate of 28 bpm and a tidal volume of 12–14 $ml \cdot kg^{-1}$. Arterial P_{CO_2} was maintained between 32 and 38 mmHg.

Arterial blood pressure was recorded through a polythene catheter placed in the right carotid artery and connected to a Gould-Statham pressure transducer. Heart rate was monitored continuously by using the arterial pulse pressure to trigger a Grass 7P4F cardiotachometer or Devices instantaneous heart rate meter. Drugs were administered through a catheter in the remaining jugular vein. Contractions of the tibialis anterior and soleus muscles were recorded by force displacement transducers (Grass FT10 or FT03). A resting tension of 30 g was applied to each muscle. Twitches were evoked every 10 s by stimulating the two branches of the sciatic nerve supplying the lower leg—immediately distal to the point where the nerve divides—using square wave pulses of 0.25 msec duration and at twice the voltage required to produce maximum contractions.

General Experimental Protocol

Initial experiments were carried out by injecting doses of the neuromuscular blocking compounds at hourly intervals until a range of neuromuscular blocks between 5 and 95% had been obtained on both the tibialis anterior and soleus muscles. Control experiments, both with the short-acting compounds tested here and with the medium duration vecuronium,[11] indicate the reproducibility of the effects of the drugs injected at different times during the course of the experiments, which lasted for a maximum of 8 h. At the end of the experiments in cats, logarithmically increasing doses of the compounds were injected at 200-s intervals until block of the vagus and nictitating membrane were obtained. The time interval of 200 s was chosen as a compromise between the generally faster action of compounds of this type on the skeletal muscles than on the cardiac vagus neuroeffector junction, with the action on the nictitating membrane often being slower still. The experiments were designed to obtain the maximum amount of comparable information from each ex-

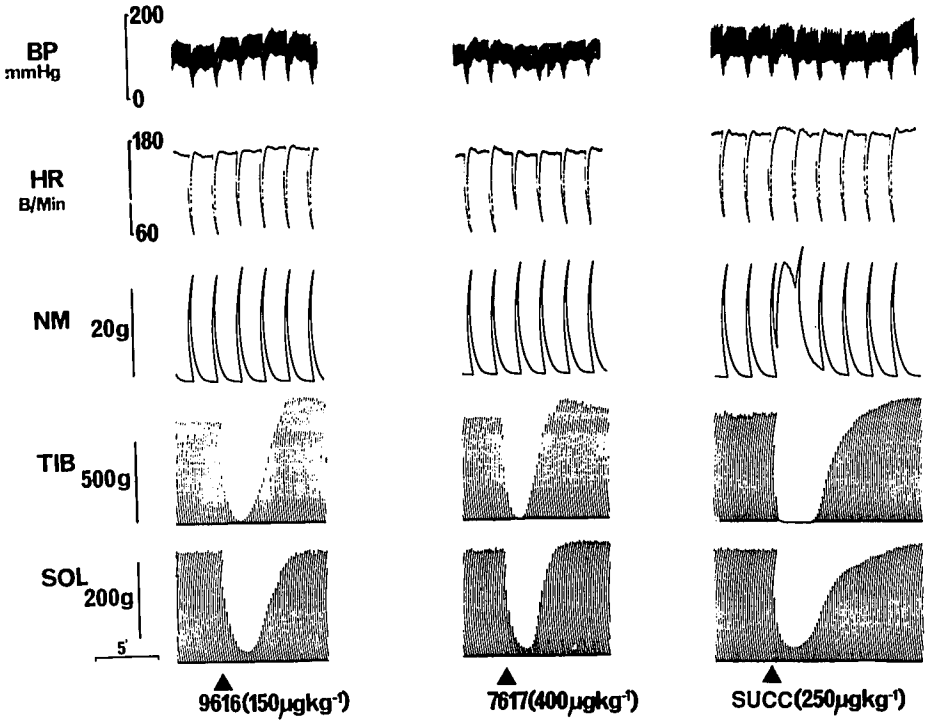


FIG. 2. Effects in a cat of Org 9616, Org 7617, and succinylcholine (SUCC) on arterial blood pressure (BP), heart rate (HR), contractions (upward deflections) of the nictating membrane (NM) to preganglionic nerve stimulation (2–5 Hz for 10 s every 100 s), and maximal contractions (upward deflections) of the tibialis anterior (TIB) and soleus (SOL) muscles evoked by stimulation of motor nerves (0.1 Hz). The right vagus nerve was stimulated every 100 s for 10 s at 5–10 Hz to produce decrease in heart rate (downward deflections of the HR trace). Induced decrease in heart rate were associated with concomitant transient reductions in arterial blood pressure.

perimental animal. From the data, dose-inhibition graphs were constructed using a non-linear iterative curve-fitting routine (Levenberg-Marquadt method) and the doses producing 50% block of the tibialis anterior, soleus, nictitating membrane, and vagus were calculated. Time courses were measured in relation to doses producing between 85 and 95% neuromuscular block. Onset time was measured as the time from injection to the first maximally depressed twitch. The recovery index was the time from 75% block to 25% block and the duration of action was the time from injection to recovery to 90% of control twitch height in both anesthetized cats and pigs. In some experiments, a dose equivalent to three times the ED_{90} was injected towards the end of the investigation to evaluate the effects of clinically relevant higher doses. In one series of experiments, the effects of ED_{90} and three times the ED_{90} twitch blocking doses of Org 7617 and Org 9616 were tested on blood pressure and heart rate in the absence of vagal or sympathetic stimulation.

Statistical Analysis

Time course data were analyzed by one-way analysis of variance and groups discriminated from one another by the Tukey-Kramer HSD test, to allow for multiple comparisons.[12] Cardiovascular changes were compared with pre-drug values and tested for significant difference using a Student's paired *t* test.

Results

General Activity

In the initial experiments, the two new compounds, Org 7617 and Org 9616, were compared with succinylcholine in both cats and pigs. In both species, Org 7617 and Org 9616 produced a short-lasting neuromuscular blockade that was not associated with pre-block twitch augmentation or with muscle fasciculations. In contrast, twitch augmentation and fasciculations were observed with succinylcholine. In some cats, but not in pigs, both Org 7617 and Org 9616 produced post-block twitch augmentation (maximum effects: Org 7617 42% tibialis, 10% soleus; Org 9616 33% tibialis, 5% soleus).

Selectivity of Action

In anesthetized cats, the compounds were tested for selectivity of action at acetylcholine receptors at the neuromuscular junction and in the autonomic nervous system by measuring their potency at the neuromuscular junction (muscle nicotinic receptors), at a sympathetic ganglion (ganglionic nicotinic receptors), and at the cardiac vagus neuroeffector junction (cardiac muscarinic receptors). The effects of approximately equieffective neuromuscular blocking doses of Org 9616, Org 7617, and succinylcholine are shown in figure 2. In this experiment, Org 9616

TABLE 1. Neuromuscular, Vagal, and Ganglion Blocking Potencies of Org 7617 and Org 9616 in Anesthetized Cats

Compound	ED_{50} ($\mu g \cdot kg^{-1}$)				$\frac{\text{Vagus } ED_{50}}{\text{Soleus } ED_{50}}$
	Tibialis	Soleus	Vagus	Nictitating Membrane	
Org 7617	287 ± 42 (12)	249 ± 31 (13)	2018 ± 255 (9)	6043 ± 273 (5)	10.3 ± 1.8
Org 9616	154 ± 17 (9)	154 ± 27 (9)	2096 ± 414 (8)	8414 ± 882 (5)	17.1 ± 3.2

ED_{50} values are expressed as mean ± SEM (n) and the vagus/soleus ratio represents the margin of safety between the two effects, calculated from the ratios obtained from individual cats.

produced only a very small effect on the chronotropic responses to vagal stimulation, slightly augmented the responses of the nictitating membrane to preganglionic stimulation, and produced a slight increase in blood pressure and heart rate. Org 7617 produced a similar effect to that of Org 9616 on the nictitating membrane, but had a rather greater blocking effect on the vagal response. Org 7617 also produced a decrease in blood pressure and heart rate. Although succinylcholine produced little effect on the vagal response or blood pressure, it produced large contractions of the nictitating membrane, presumably either as a result of ganglion stimulation or of a direct muscarinic action on the nictitating membrane.

The doses of Org 7617 and Org 9616 producing 50% block of the responses of the tibialis and soleus muscles, of the heart rate response to vagal stimulation, and of the preganglionically stimulated nictitating membrane are shown in table 1. From this table, it can be seen clearly that both compounds primarily affect the neuromuscular junction, Org 9616 being approximately twice as potent as Org 7617 as a neuromuscular blocker. The two compounds were approximately equieffective on the tibialis anterior and soleus muscles. At doses of 2 $mg \cdot kg^{-1}$ of both compounds, 50% vagal block was seen. The vagal/neuromuscular block ratio, *i.e.*, a measure of the margin of safety between the neuromuscular blocking and the unwanted vagal blocking actions, is also shown in table 1. Doses of 5–10 $mg \cdot kg^{-1}$ were required to block the nictitating membrane. In a small number of experiments, contractions of the nictitating membranes to both pre- and postganglionic stimulation were recorded. Both Org 7617 and Org 9616, in doses that blocked responses to preganglionic stimulation, produced no block but, rather, an augmentation of the responses to postganglionic stimulation.

TIME COURSE OF NEUROMUSCULAR BLOCK

The time course of the neuromuscular block produced by Org 7617, Org 9616, and succinylcholine at approximately 90% twitch block was assessed in both cats and pigs (table 2). Org 7617 and Org 9616 were virtually equipotent on the tibialis and soleus muscles in the cat. In contrast, succinylcholine in both cat and pig, and Org 7617 and Org 9616 in the pig, were two to three times more potent on the tibialis muscle than on the soleus muscle. In both the cat and the pig, the onset, recovery index, and duration of action of Org 7617 were not significantly different from those of Org 9616. In the cat, the values were, overall, slightly shorter than the corresponding values for succinylcholine. However, in the pig, the time course values overall were slightly longer than those of succinylcholine. The effects of three times the dose of each of the three drugs producing 90% twitch depression on the tibialis muscle of the pig were compared. In these experiments, in addition to the onset time, recovery index, and duration of action, the duration of complete twitch blockade was measured. The results are shown in figure

TABLE 2. Time Course of Neuromuscular Blockade (Mean ± SEM) (n) Following the iv Injection of Approximate ED_{90} Blocking Doses of Succinylcholine (succ), Org 7617, and Org 9616 in both the Tibialis Anterior and Soleus Muscles of Anesthetized Cats and Pigs

Species	Compound	Dose ($\mu g \cdot kg^{-1}$)		Onset (Min)		Recovery 25–75% (Min)		Duration 90% (Min)	
		Tibialis	Soleus	Tibialis	Soleus	Tibialis	Soleus	Tibialis	Soleus
Cat	succ	58 ± 10 (10)	183 ± 30 (6)	1.7 ± 0.1	3.2 ± 0.2	1.9 ± 0.3	3.4 ± 0.5	5.7 ± 0.6	10.6 ± 0.9
	Org 7617	560 ± 75 (5)	530 ± 83 (5)	1.6 ± 0.1	2.4 ± 0.3*	0.8 ± 0.2*	1.3 ± 0.1*	3.9 ± 0.4	6.2 ± 0.6*
	Org 9616	203 ± 40 (5)	181 ± 26 (5)	1.5 ± 0.1	2.4 ± 0.1*	1.0 ± 0.1*	1.6 ± 0.2*	4.3 ± 0.3	6.9 ± 0.7*
Pig	succ	783 ± 136 (6)	1303 ± 153 (7)	1.0 ± 0.1	1.6 ± 0.2	0.8 ± 0.1	1.8 ± 0.1	2.6 ± 0.4	5.5 ± 0.5
	Org 7617	794 ± 79 (8)	2325 ± 145 (6)	1.1 ± 0.1	2.4 ± 0.1*	1.9 ± 0.1*	3.1 ± 0.5	5.5 ± 0.3	10.6 ± 1.3*
	Org 9616	421 ± 19 (6)	1089 ± 120 (6)	1.2 ± 0.1*	2.4 ± 0.2*	2.1 ± 0.1*	3.6 ± 0.5*	6.5 ± 0.3*	11.6 ± 1.3*

No significant differences between Org 7617 and Org 9616 groups. * $P < 0.05$ significantly different from succinylcholine.

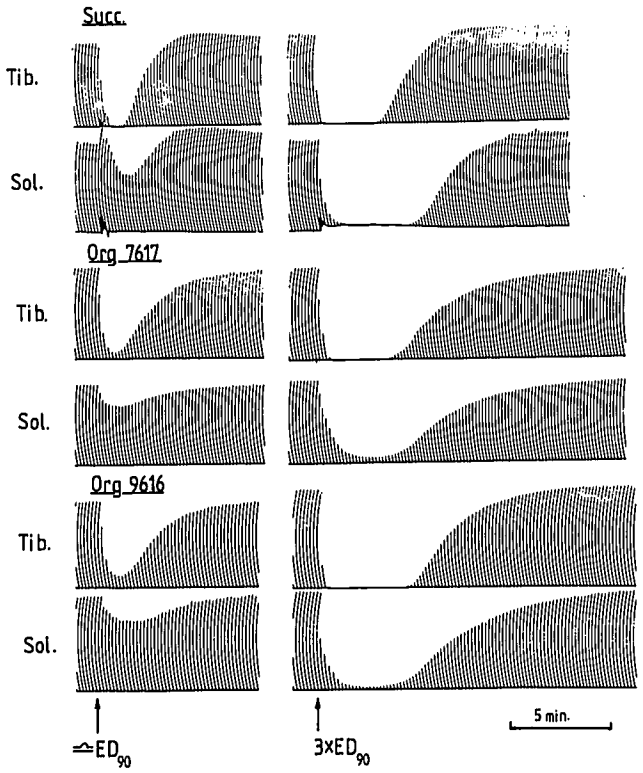


FIG. 3. Effects in anesthetized pigs of succinylcholine (Succ), Org 7617, and Org 9616 on contractions of the tibialis (Tib) and soleus (Sol) muscles evoked by electrical stimulation of motor nerves. Neuromuscular blocking profiles shown are at doses (700, 600, and 450 $\mu g \cdot kg^{-1}$) producing approximately 90% twitch depression (ED_{90}) and at three times ED_{90} ($3 \times ED_{90}$) blocking doses (2045, 2250, and 1420 $\mu g \cdot kg^{-1}$ Succ, Org 7617, and Org 9616, respectively) calculated by linear regression analysis of inhibition data from the tibialis muscle.

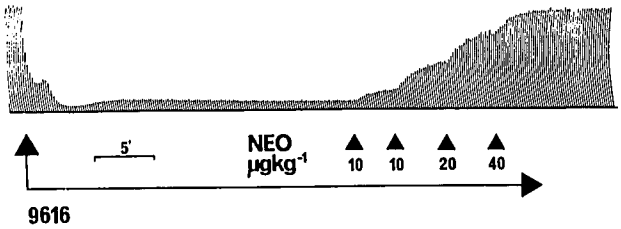


FIG. 4. Antagonism of Org 9616 by cumulative administration of neostigmine. Org 9616 was administered by infusion to maintain neuromuscular block of the soleus (cat) at 90–95%. In this example, using regression line analysis, a total dose of 23.5 $\mu g \cdot kg^{-1}$ neostigmine produced 50% restoration of neuromuscular function.

3 and table 3. With these large doses, the onset times of the three drugs became uniformly fast, whereas the recovery and duration times were two to three times longer than those following the 90% blocking doses. Org 7617 produced a duration of complete block not significantly different from that produced by succinylcholine, whereas that produced by Org 9616 was longer. Otherwise, the duration and recovery times of both Org 7617 and Org 9616 were significantly longer than the equivalent times for succinylcholine.

REVERSIBILITY OF NEUROMUSCULAR BLOCK

To avoid the problems of interpreting the effects of anticholinesterases injected at the height of neuromuscular block produced by bolus administration of short-acting compounds, reversibility was assessed during steady-state block maintained by infusion. Org 7617 and Org 9616 were initially injected in a bolus dose sufficient to produce approximately 90% twitch blockade on the cat soleus muscle. Ninety to 95% twitch block was then maintained by constant infusion for at least 15 min. Incremental doses (10, 10, 20, and 40 $\mu g \cdot kg^{-1}$) of neostigmine were then administered at 2–3-min intervals until a maximum level of recovery of twitch height was observed. The infusion of the neuromuscular blocking drug was maintained until after the maximum effects of the anticholinesterase were observed. The effects of both Org 7617 and Org 9616 were readily reversed by neostigmine (fig. 4). ED_{50} values for the neostigmine calculated from the dose-response lines were 24 ± 6 $\mu g \cdot kg^{-1}$ (n = 3) for Org 7617 and 41 ± 9 $\mu g \cdot kg^{-1}$ for Org 9616 (n = 3). A comparable value for vecuronium obtained under similar experimental conditions was 19 ± 4 $\mu g \cdot kg^{-1}$ (n = 3).

TABLE 3. Time Course of Neuromuscular Block (Tibialis Muscle) Following the Injection of Three Times Calculated ED_{90} Blocking Doses of Succinylcholine, Org 7617, and Org 9616 in Anesthetized Pigs

Compound	Dose ($\mu g \cdot kg^{-1}$)	% Blockade	Mean Duration of Complete Block (Min)	Onset* (Min)	Recovery 25–75% (Min)	Duration 90% (Min)
Succinylcholine n = 6	2230 ± 154	100	2.8 ± 0.4‡	0.6 ± 0	1.8 ± 0.2	7.4 ± 0.5
Org 7617 n = 6	2325 ± 145	100	2.8 ± 0.1‡	0.7 ± 0	3.7 ± 0.4†	12.3 ± 1.2†
Org 9616	1291 ± 62	100	4.2 ± 0.2	0.6 ± 0	3.3 ± 0.4†	12.8 ± 1.3†

* Onset time from injection to 100% inhibition of twitch tension.
† $P < 0.05$ significantly different from succinylcholine.
‡ $P < 0.05$ significantly different from Org 9616.

TABLE 4. Maximum Effects of Org 7617 and Org 9616 on Mean Arterial Blood Pressure and Heart Rate (Mean ± SEM) in Anesthetized Cats and Pigs

Species	Compound	ED_{90} Blocking Doses						$3 \times ED_{90}$ Blocking Doses					
		Blood Pressure (mmHg)			Heart Rate (Beats/Min)			Blood Pressure (mmHg)			Heart Rate (Beats/Min)		
		Pre	Post	%	Pre	Post	%	Pre	Post	%	Pre	Post	%
Cat	Org 7617 n = 5	58 ± 4	47 ± 3*	−19	135 ± 7	135 ± 7	0	57 ± 8	33 ± 3*	−42	131 ± 10	128 ± 9	−2
	Org 9616 n = 5	61 ± 7	60 ± 6	−2	182 ± 38	182 ± 37	0	58 ± 6	62 ± 6	+7	172 ± 32	174 ± 34	+2
Pig	Org 7617 n = 6	90 ± 8	68 ± 5†	−24	115 ± 4	112 ± 3	−3	82 ± 7	52 ± 3†	−37	116 ± 5	107 ± 4	−8
	Org 9616 n = 6	81 ± 6	75 ± 5*	−7	119 ± 5	122 ± 5	+3	80 ± 7	60 ± 4†	−25	110 ± 7	112 ± 6	+2

Significantly different from pre-drug values using paired *t* test. *$P < 0.05$; †$P < 0.01$.

EFFECTS ON BLOOD PRESSURE AND HEART RATE

In both the cat and the pig, Org 7617 produced a consistent dose-related decrease in blood pressure with little or no effect on heart rate except at high doses in the pig. In contrast, the effects of Org 9616 were less consistent with no overall change of heart rate or blood pressure in cats. In the pig, Org 9616 produced a small decrease in blood pressure with a similar time course to that produced by Org 7617 (table 4).

Discussion

The aim of the present study is to identify potential drug candidates for clinical trial as short-acting nondepolarizing muscle relaxants. Our strategy has been to use the anesthetized cat as a predictor of potency and onset of neuromuscular block, and of possible autonomic side effects. The onset times of previously tested aminosteroids in this series that have been evaluated clinically (pancuronium, vecuronium, dacuronium, and Org 6368) have shown a reasonable correlation with onset times in cats. The vagal/neuromuscular block ratio in the cat is regarded as a useful measure of the propensity of a compound to produce tachycardia in humans as a result of block of cardiac muscarinic receptors.[13–16] We have used the anesthetized pig as a potential predictor of the time course of action of the drugs and of cardiovascular side effects inasmuch as it has been shown previously that the pig was predictive of these effects in a small series of pancuronium analogues that had been tested in several species, including humans.[17]

Succinylcholine exhibited the typical properties of a depolarizing drug, producing muscle fasciculations and pre-block twitch augmentation. Succinylcholine was much more potent in cats than it was in pigs. The potency in humans is intermediate. Org 9616 and Org 7617 showed neither pre-block twitch augmentation nor fasciculations, although, in the cat, they did produce a period of post-block twitch augmentation. The effects of both new compounds were readily reversed by neostigmine. Additionally, in isolated avian muscle, which responds to depolarizing agents with a sustained contracture,[18] Org 9616 and Org 7617 produced neuromuscular block without contracture.[¶] We have thus concluded that, like other aminosteroids in this series, Org 9616 and Org 7617 produce block by a nondepolarizing mechanism.

The previously studied compounds in the pancuronium series that showed short action in cats, but not in humans or pigs, were bisquaternary compounds. We have now examined a series of monoquaternary vecuronium analogues and Org 7617 and Org 9616, both 17-butyrates, represent promising examples. Our criteria for selection of these compounds were a time course similar to that of succinylcholine, a potency similar to or greater than that of d-tubocurarine, and a low level of autonomic and cardiovascular side effects. In general, in this series, there is an inverse correlation between neuromuscular blocking potency and rapidity of action, *i.e.*, the more potent the compound, the slower its action.[19] In accordance with this, the short-acting compounds that we have tested are approximately one-fifth to one-tenth the potency of vecuronium[20] at the neuromuscular junction, but are approximately equipotent with vecuronium at the cardiac vagus neuroeffector junction. Thus, inevitably, in these new compounds, there is a lower margin between the required neuromuscular blocking action and the unwanted vagal blocking action (vagal:neuromuscular ratios;

¶ Green KL: Studies on the mechanisms of action of some newly synthesised quaternary steroidal neuromuscular blocking compounds Ph.D. thesis, University of Strathclyde, 1987, 266 pp.

Org 9616 17, Org 7617 10) than that seen with vecuronium (vagal:neuromuscular ratio 63–84).[20–22] However, the ratios between neuromuscular and vagal block for Org 9616 and Org 7617 are greater than those for pancuronium[13,21] and are similar to those for agents such as metocurine and atracurium.[13,22–24] The use of metocurine and atracurium in humans has not been associated with significant tachycardia.[25,26] Thus, it might be predicted that cardiovascular side effects as a result of vagal block are unlikely to be seen.

The most consistent cardiovascular side effect that we did observe in both cats and pigs was the dose-related hypotensive action of Org 7617. We consider it unlikely that this effect is a result of sympathetic ganglion block, as it was observed at doses around one-fifteenth that which caused block of the preganglionically stimulated nictitating membrane. In addition, a role of histamine in Org 7617-induced hypotension seems unlikely, since this effect of Org 7617 is not modified by histamine (H_1 and H_2) antagonists in anesthetized rats (our unpublished data). Preliminary experiments in isolated potassium precontracted rat aortic strips have shown that Org 7617 possesses a direct relaxant effect (ED_{50} 3 μM), which is possibly mediated by block of calcium channels, and this would seem the most likely mechanism underlying the hypotensive effect of Org 7617 in whole animals.

The observed augmentation of the postganglionically stimulated nictitating membrane by Org 7617 and Org 9616 does not appear to be due to either a prejunctional α_2-adrenoceptor antagonism or to inhibition of norepinephrine reuptake into sympathetic nerve terminals (our unpublished data). It is, however, possible that, in common with pancuronium, these compounds may possess a weak tyramine-like action to promote the release of norepinephrine from nerve endings.[27]

As we have indicated previously, the time course of action of nondepolarizing relaxants in anesthetized cats is not necessarily a good guide to their time course in humans. Nevertheless, it is of note that both Org 7617 and Org 9616 were at least as short-acting as succinylcholine in cats. In anesthetized pigs, Org 7617 and Org 9616 were somewhat longer in time course than succinylcholine, but were still considerably shorter in action than vecuronium and pancuronium, and than Org 6368, which has a short duration of action in cats.[17,28] In both species, the onset time of the new compounds was one-half to one-third that of vecuronium, and the duration of action was approximately one-half that of vecuronium. Thus, we would predict that Org 7617 and Org 9616 would have a duration of action in humans only slightly longer than that of succinylcholine. In particular, it is noteworthy that the percentage increase in duration with a large (3 × 90% blocking) dose was actually less for Org 7617 and Org 9616 than it was for succinylcholine. In addition to the favorable time courses exhibited by Org 7617 and Org 9616, the neuromuscular blocking effects of both compounds were readily antagonized by neostigmine.

We conclude that the two new monoquaternary steroidal compounds, Org 7617 and Org 9616, represent potential examples of short-acting nondepolarizing muscle relaxants with acceptable autonomic and cardiovascular side effects.

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