

# Modification of Atracurium or Vecuronium Blockade and Their Reversal by Succinylcholine in the Cat

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*The interaction between succinylcholine (SCC) and non-depolarizers, atracurium or vecuronium was investigated in 36 cats of either sex using the sciatic nerve-anterior tibialis muscle preparation. Additionally, the relation of SCC to pseudocholinesterase activity was examined.*

*The duration of action of vecuronium ( $6.5 \pm 1.3$  to  $7.3 \pm 2.2$  minutes) in cats pretreated with SCC was greater than those ( $2.0 \pm 0.6$  minutes) in non-pretreated cats. However, SCC had no influence on the duration of atracurium. The serum pseudocholinesterase activity was decreased after the injection of atracurium or neostigmine in contrast to vecuronium.*

*The authors conclude that the prior administration of SCC prolongs the duration of vecuronium but not that of atracurium, and pseudocholinesterase activity is not related to the prolonging effect of SCC.*

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**Key Words:** Neuromuscular relaxants; succinylcholine, atracurium, vecuronium; Pharmacodynamics; interaction

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Prior administration of succinylcholine (SCC) may increase the twitch-depressing effect of non-depolarizing agents. The duration of the non-depolarizing neuromuscular blocking agent is frequently prolonged, especially in patients who received SCC for endotracheal intubation followed immediately by a non-depolarizing agent for surgical manipulation.

It has been demonstrated that the prior injection of SCC augments the action of non-depolarizing agents, such as d-tubocurarine (Katz et al. 1981), pancuronium (Katz, 1971), vecuronium (Krieg et al. 1981) and atracurium (Stirt et al. 1983). The effect of SCC on the action of non-depolarizing agents may at the first glance seem contradictory to the generally accepted idea of an antagonism between the depolarizing and non-depolarizing agents in previous studies.

However, there is still controversy about whether or not the duration of non-depolarizing agents is prolonged by the preceding bolus injection of SCC, and whether or not the time interval between SCC and a non-depolarizing agent is related to the potentiation of action of the consecutive non-depolarizer.

This study proposed a comprehensive evaluation with different time intervals of the influences of the preceding SCC administration on the neuromuscular blocking effect of the consecutive administration of atracurium and vecuronium in the cat.

## METHODS

### Animal and Surgical Preparation

Thirty-six cats of either sex premedicated with 10-15 mg/kg of ketamine subcutaneously. Anesthesia was induced with intravenous injection of 3 mg/kg of pentobarbital and maintained under the intravenous infusion of pentobarbital (3 mg/kg/hr).

Tracheostomy was performed and ventilation was controlled to maintain  $\text{PaCO}_2$  at 35 to 45 mmHg

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with the tidal volume of 12 ml/kg and the respiration rate of 35-45 cycles/min using a Respiration pump (Model 607 Harvard® animal ventilator). The external jugular vein and the internal carotid artery were cannulated to administer drugs and monitor the arterial pressure, respectively.

To monitor neuromuscular function, the tendon of the anterior tibialis muscle was isolated and its distal end was attached to a Grass FT-10 force-displacement transducer. The sciatic nerve was dissected and stimulated with a supramaximal square wave impulse of 0.2 msec duration at 0.1 Hz, applied via platinum electrodes, and the contractile force of the anterior tibialis muscle was recorded on a Grass® model 79E polygraph.

### Experimental Design

The study was divided into two groups and group II was subdivided into two subgroups.

#### Group I. Cumulative dose-response curves of atracurium or vecuronium without SCC

The purpose of this group was to determine the cumulative dose-response curve of atracurium and vecuronium without SCC in order to establish the ED<sub>95</sub> (ie. dose which depressed twitch tension by 95%). An initial dose of atracurium, 50 µg/kg (n=6) or vecuronium, 20 µg/kg (n=6) was administered intravenously. Further identical doses were administered whenever the two or three successive identical twitch tensions had occurred. Doses were repeated until the force of contraction of the muscle had decreased by 95%. A preliminary dose-response curve was constructed. The probit transform of the percent depression in the force of muscle contraction versus the logarithm scale of the cumulative dose of atracurium or vecuronium were compared by least squares linear regression. From the resulting regression equations, the theoretical doses of atracurium or vecuronium producing 50% and 95% depression of the force of the muscle contraction were calculated. These were used to guide dosing in group II.

#### Group II. Single bolus injection of atracurium or vecuronium at different time intervals following preceding SCC administration.

The group had 2 subgroups, according to the injection time of atracurium or vecuronium, following preceding SCC administration.

Ila (n=6); when the twitch tension revealed

zero after the administration of 150 µg/kg of SCC.

Ilb (n=6); when the twitch depression due to 150 µg/kg of SCC was recovered to the twitch height at preadministration.

The onset time (the time from the end of injection to the maximum effect), the duration (the time from the maximum effect to the recovery to 25% twitch tension), recovery index (the time of spontaneous recovery from 25% to 75% twitch tension) and antagonism time (the time from the injection of neostigmine to 100% recovery of the twitch tension) were measured. The onset time was measured only in group IIb and the others in all groups. Neostigmine was injected consistently at the 75% recovery of twitch tension.

Pseudocholinesterase (PchE) activity was measured when no relaxant was administered, at the maximum neuromuscular effect of the non-depolarizing agent and after the injection of neostigmine. The colorimetric method (Ellman et al. 1961) was used with acetylthiocholine as a substrate.

From the small doses given initially to achieve 95% depression of twitch tension, a preliminary dose-response curve was constructed in group I.

The probit transform of the percent depression of twitch tension versus the logarithm of the cumulative dose of atracurium or vecuronium were compared by least squares linear regression. From the resulting regression equations, the theoretical doses of atracurium or vecuronium producing 50% and 95% depression of twitch tension were calculated.

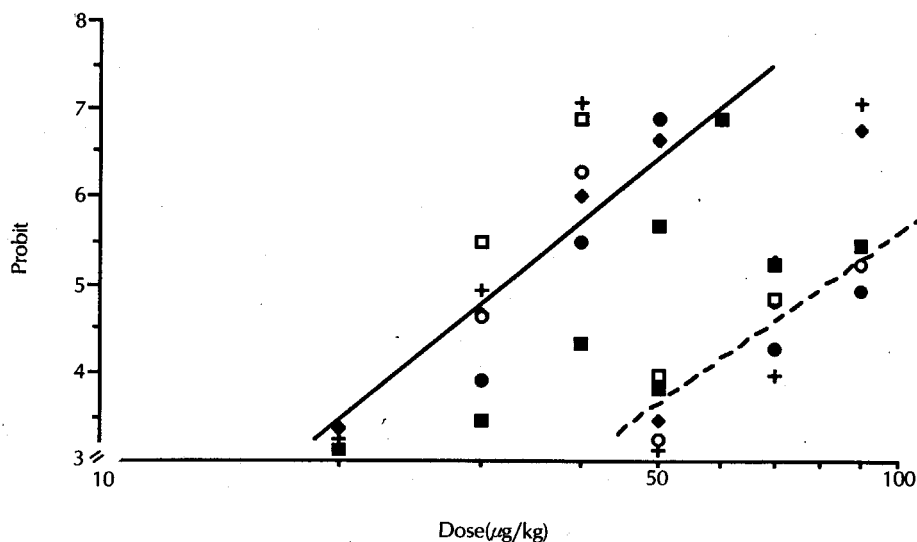
These were used to guide dosing in group II.

The onset, duration, recovery index, antagonism time and PchE activity among groups were compared to each group by ANOVA and Kruskal-Wallis test followed by multiple non-parametric comparison. For all statistical comparison, differences were considered significant when  $p < 0.05$ .

## RESULTS

The ED<sub>95</sub> of atracurium and vecuronium were  $101.3 \pm 11.6$  and  $43.7 \pm 4.3$  µg/kg, respectively. They were calculated from individual dose-response relationships in group I (Fig. 1, Table 1), and used to define the onset, duration, recovery index and antagonism time in group II.

The onset of action by ED<sub>95</sub> of atracurium and



**Fig. 1.** Cumulative dose-response curves with vecuronium (—,  $y=0.794+2.922x$ ,  $r=0.959$ ) and atracurium (-----,  $y=2.959+0.777x$ ,  $r=0.849$ ) in group (n=12). Each legend represents the individual cat which three different doses were administered.

**Table 1.** ED<sub>50</sub> and ED<sub>95</sub> of atracurium and vecuronium for muscle relaxation with cumulative dose-responses in the cat (Mean±SD, μg/kg)

Agent	Dose	
	ED <sub>50</sub>	ED <sub>95</sub>
Atracurium	74.5±6.6	101.3±11.6
Vecuronium	32.6±3.1	43.7±4.3

vecuronium in group IIb were  $2.3 \pm 0.7$  and  $1.9 \pm 0.4$  minutes, respectively (Table 2). Due to the experimental design in group IIa the onset of action could not be obtained. The duration of action by ED<sub>95</sub> of vecuronium was significantly longer in group IIa and IIb ( $6.5 \pm 1.3$  and  $7.3 \pm 2.2$  minutes, respectively) than in group I ( $2.0 \pm 0.6$  minutes) ( $p < 0.05$ ). With atracurium, the duration of action was not influenced by preceding SCC administration even though the duration by ED<sub>95</sub> was longer in group IIa than group IIb.

**Table 2.** Comparison of onset and duration among groups

		Mean±SD (min)			
Group \ Agent		Onset		Duration	
		Atracurium	Vecuronium	Atracurium	Vecuronium
I				$3.1 \pm 1.2$	$2.0 \pm 1.2$
IIa				$3.9 \pm 2.3^*$	$6.5 \pm 1.3^{\dagger}$
IIb		$2.3 \pm 0.7$	$1.9 \pm 0.4$	$1.8 \pm 1.0$	$7.3 \pm 2.2^{\dagger}$

\*  $p < 0.05$  group IIa vs IIb in atracurium.

$^{\dagger}$   $p < 0.05$  group IIa & IIb vs I in vecuronium.

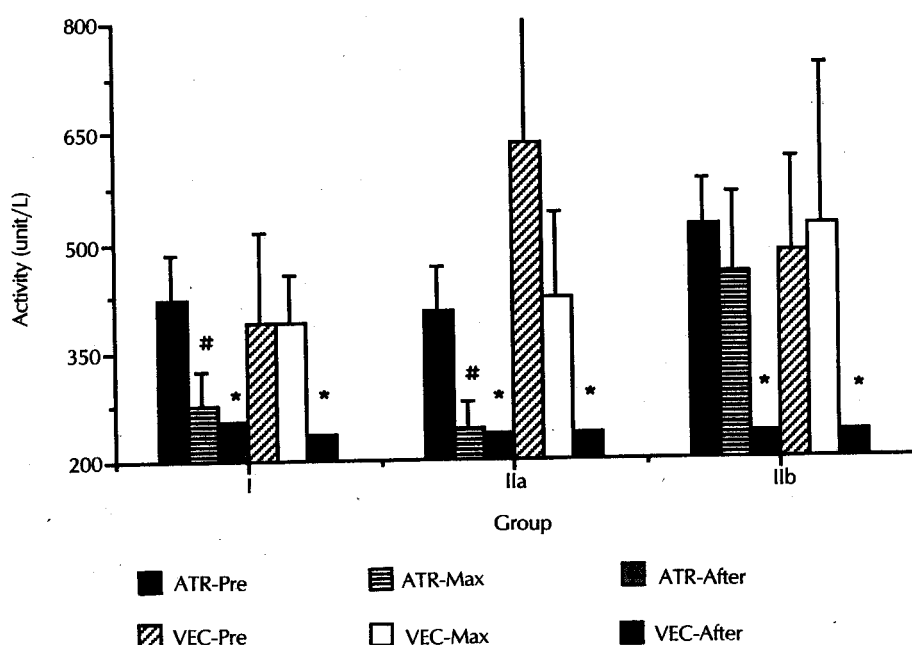
Group I was not pretreated with SCC. In group IIa and IIb, each non-depolarizer was given at the time when the twitch tension after SCC revealed zero and the twitch depression was recovered to the pre-administration level, respectively.

**Table 3. Recovery index and antagonism time of atracurium or vecuronium in each group** Mean  $\pm$  SD (min)

Group \ Agent	Atracurium		Vecuronium	
	Recovery index	Antagonism time	Recovery index	Antagonism time
I	3.5 $\pm$ 1.3	3.8 $\pm$ 1.7	2.1 $\pm$ 0.6	3.0 $\pm$ 1.2
Ila	3.6 $\pm$ 1.7	2.5 $\pm$ 1.0	2.5 $\pm$ 0.7	1.6 $\pm$ 0.4
Ilb	2.8 $\pm$ 0.9	2.2 $\pm$ 0.9	2.7 $\pm$ 0.6	2.0 $\pm$ 0.3

Recovery index and antagonism time represent the time which the twitch is recovered from 25% to 75% and from 75% to 100% after neostigmine injection, respectively.

Group I was not pre-treated with SCC. In group Ila and Ilb, each non-depolarizer was given at the time when the twitch tension revealed zero and the twitch depression was recovered to the pre-administration level, respectively.



**Fig. 2.** Pseudocholinesterase activities were compared by the different time sequences.

Pre, Max and After represent the time prior to the injection of agents, at the maximum effects of relaxants and after the injection of neostigmine, respectively.

ATR and VEC represent atracurium and vecuronium, respectively.

Neither atracurium nor vecuronium had significant difference in recovery indices and antagonism times in respect to preceding SCC (Table 3).

PchE activity was not significantly changed after the administration of vecuronium in contrast to atracurium. However, there was significant change of pseudocholinesterase activity after the administration of neostigmine in all groups with either

agent.

Atracurium reduced pseudocholinesterase activity in group I and Ila, but, not in group Ilb (Fig. 2).

## DISCUSSION

This study aimed to evaluate the prolongation of

a non-depolarizing agent, atracurium or vecuronium. It was revealed that the duration of action of vecuronium was significantly prolonged, but that of atracurium was not. The speed of recovery in aspect of the recovery index and antagonism from the block was not altered following SCC administration in both agents.

The duration of non-depolarizing agents following SCC administration is controversial in regards to the degree of prolongation and its mechanism. Foldes *et al.* (1957) observed a potentiation effect after SCC infusion on d-tubocurarine in dogs and cats, and also Krieg *et al.* (1981) found a potentiation and prolonged recovery of a bolus of 36  $\mu\text{g}/\text{kg}$  if administered after complete recovery from 1 mg/kg of SCC with bolus injection. Although this study was done only in cats, this prolongation response was comparable with their results.

However, no increase in atracurium block duration was noted following previous SCC administration in our study. There was a difference of the duration of atracurium between group IIa and IIb.

However, the onset time was added to the duration in group IIa as the interval from the injection to the recovery of 25% twitch tension. This result is in close agreement with that by Stirt *et al.* (1983), while Donati *et al.* (1991) found in their result, that less atracurium is required for an equivalent degree of block following prior administration of SCC due to the altered pharmacokinetics of atracurium. There are many factors which influence the results. It may be included that the individual agent, the applied species, the time interval between SCC and a non-depolarizer, and the technique of administration are just some of the variable factors.

For the other non-depolarizing agents, several report show conflicting results. For example, which there was effects of SCC on pancuronium (Katz, 1971), vecuronium (D'Hollander *et al.* 1983) and d-tubocurarine (Katz *et al.* 1969), while there were no effects on pipecuronium (Dubois *et al.* 1991; Chae 1987), d-tubocurarine (Waltz and Dillon 1969) pancuronium (Waltz and Rusin 1977) and doxacurium (Katz *et al.* 1988; Lynam *et al.* 1988).

We attempted to define the relationship between the injection time and the degree of the SCC-induced potentiation of the non-depolarizing agent. The same degree of the prolongation was noted following vecuronium administration when the twitch tension after SCC was either zero or complete recovery to the initial twitch tension. D'Hollander *et al.* (1983) suggested clinically the decrease in dose could be applicable for 30 minutes past

after clinical recovery from the neuromuscular blockade induced by SCC in view of the potentiation of vecuronium even if 30 minutes after complete recovery following SCC administration. Within this time, there was no difference in duration of the non-depolarizing agent. The two time intervals in the present study were included within 30 minutes after SCC administration.

Although several opinions are suggested, the mechanism for the potentiating effect of SCC on non-depolarizing agents is not clear.

They include the reduction in the rate of degradation of vecuronium in the plasma (Krieg *et al.* 1981), a decreased sensitivity of the end-plate (Foldes *et al.* 1957) and an increase in end-plate sensitivity to atracurium (Donati *et al.* 1991). Waud and Waud (1985) suggested theoretically an interaction of acetylcholine receptors due to their interaction. We could not find this mechanism with our experimental design.

The  $\text{ED}_{50}$  of atracurium was smaller in our study than in a previous report (Sutherland *et al.* 1983), while that of vecuronium is in close agreement. Cumulative dose-response technique tends to require higher doses to produce equivalent blockade, most likely because of the relatively rapid elimination and redistribution of these drugs during administration of incremental doses (Smith *et al.* 1988). And so, the difference in atracurium could not be explained with our results. Another reason, generally, may be that acidosis results subsequently, decreasing the rate of Hoffman's elimination in atracurium. However, there was slight alkalosis on our experimental animals.

PChE activity can be changed by many conditions. It may be considered that the effect of SCC is attenuated by decreased PChE activity (Jorgen 1980), which may be induced by non-depolarizing agents (Katz 1971; Stovner *et al.* 1975). Our results revealed that a remarkable decrease of PChE activity occurred after the administration of neostigmine in all groups and atracurium only in group I and IIa, but not in vecuronium. This would indicate there is no relation to the prolongation of vecuronium block.

The recovery from atracurium or vecuronium was not influenced by 150  $\mu\text{g}/\text{kg}$  of bolus SCC in this study in respect to recovery index and complete recovery from 75% twitch tension by injection of neostigmine. With doxacurium (Lynam 1988) and pipecuronium (Dubois 1991), there was no effect on the recovery index and antagonism.

The authors conclude that the duration of

vecuronium is prolonged by preceding SCC, whenever it is administered either at SCC-induced maximum depression or after complete recovery and this was not true in atracurium. For defining the relationship between the time interval and prolongation, further studies with more time intervals are needed.

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