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Edrophonium Antagonizes Combined Lidocaine–Pancuronium and Verapamil–Pancuronium Neuromuscular Blockade in Cats

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The effects of lidocaine or verapamil on pancuronium neuromuscular blockade and the ability of anticholinesterase agents to antagonize these combined blockades were studied in 14 cats using a standard peroneal nerve–anterior tibialis muscle preparation. Pancuronium was infused at a constant rate to produce a stable 50% depression of single twitch tension. In nine cats, intravenous lidocaine boluses followed by a constant infusion produced serum lidocaine levels of 5.09 ± 1.9 μg/ml (mean ± SD) and resulted in an additional 20.0 ± 5.5% depression of twitch tension. In the other five cats, intravenous injection of 0.15 mg/kg of verapamil produced an additional 12.8 ± 8.0% twitch depression of pancuronium-induced neuromuscular blockade. For individual animals, edrophonium antagonism of the combined lidocaine–pancuronium–induced neuromuscular blockade or combined verapamil–pancuronium–induced neuromuscular blockade was not significantly different from antagonism of an equivalent twitch depression produced by pancuronium alone. It is concluded that lidocaine and verapamil augment neuromuscular blockade caused by pancuronium and that anticholinesterase antagonism of this augmented blockade can be expected to occur in a normal fashion. (Key words: Drug interactions: lidocaine; pancuronium; verapamil. Neuromuscular antagonists: edrophonium. Neuromuscular relaxants: pancuronium.)

CLINICAL REPORTS have suggested the possible potentiation of neuromuscular blockade by the antiarrhythmic drugs lidocaine[1] or verapamil.[2] Laboratory experimentation has shown potentiation to occur with both drugs. Lidocaine blood levels three to five times higher than those used clinically in humans produce significant increases in pancuronium–induced neuromuscular blockade.[3,4] Administration of the calcium channel blocking agent verapamil has been shown to reduce twitch tension by 10–30% in animals[5,6] and to potentiate pancuronium-induced neuromuscular blockade.†‡ The antagonism of combined lidocaine–pancuronium– or verapamil–pancuronium–induced neuromuscular blockade has not been studied. We superimposed lidocaine and verapamil intravenous infusions on constant pancuronium infusions in cats to determine their effect on neuromuscular blockade, and we also determined the ability of edrophonium to antagonize the resulting neuromuscular blockade.

Materials and Methods

Following approval by the Animal Experimentation Committee, 14 cats, weighing 2.2–6.0 kg, were anesthetized with ketamine 20 mg/kg im followed by intravenous chloralose (75 mg/kg) and urethane (375 mg/kg). The trachea was intubated. End-tidal CO_2 was continuously monitored, and arterial blood gases were serially monitored. Room air ventilation was controlled to maintain arterial P_{CO_2} between 31–35 mmHg and *p*H at 7.25 ± 0.3 (mean ± SD). Esophageal temperature was recorded and maintained between 37.8 and 39.1° C.

The carotid artery was cannulated and arterial pressure continuously monitored. The external jugular, cephalic, and femoral veins were cannulated, and each intravenous line was used exclusively for a single drug infusion.

The tendon of the anterior tibialis muscle was sectioned and attached to a Grass® FT-03 force displacement transducer. The peroneal nerve was isolated, and supramaximal stimulation (4–24 v) of 0.2 ms duration and 0.1 Hz was applied by a Grass® SD-9 nerve stimulator through shielded platinum electrodes. Muscle contractions were continuously recorded on a Beckman® R611 polygraph. Twitch height was linearly proportional to the isometric force of contraction. A stable baseline muscle twitch was obtained with 20–25 g of resting tension.

The effect of lidocaine on pancuronium neuromuscular blockade was studied in nine animals. A pancuronium infusion was begun and then adjusted to produce a stable 50% depression of twitch tension for at least 15 min (fig. 1). The pancuronium infusion varied from 0.46 to 1.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$, reflecting individual animal sensitivities. While this rate of pancuronium infusion was continued, lidocaine was administered intravenously as follows: bolus 1.5 mg/kg and a constant infusion of 60 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were administered, followed 1.5 min later by a second bolus of 1.0 mg/kg. Serum lidocaine levels and the extent of further twitch depression were measured after a 30-min period while the pancuronium and lidocaine infusions were continued. The significance of augmentation of blockade by lidocaine was assessed by paired *t* test. In five of the nine cats, the combined neuromuscular block was then antagonized with three doses of edrophonium, 10 μg/kg each, given over a period of 1–1.5 min so as to have a cumulative effect and approximate a dose–response

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† Kraynack BJ, Lawson NW, Gintautas J: Verapamil reduces indirect muscle twitch amplitude and potentiates pancuronium *in vitro* (abstract). ANESTHESIOLOGY 57:A265, 1982.

‡ Durant NN, Nguyen N, Briscoe JR, Katz RL: Potentiation of pancuronium and succinylcholine by verapamil (abstract). ANESTHESIOLOGY 57:A267, 1982.

curve. The resultant antagonism of twitch depression was calculated as a percentage of the preexisting depression. For example, if twitch tension was depressed 20 mm from baseline and edrophonium administration caused a 10 mm antagonism (twitch tension depressed only 10 mm), the edrophonium would have caused a 50% antagonism of twitch depression (*i.e.*, 10 mm/20 mm · 100%).

Immediately following edrophonium reversal, serum lidocaine concentration again was measured. The lidocaine was then discontinued and twitch tension allowed to return to the 50% depression associated with the ongoing pancuronium infusion. The total duration of the lidocaine infusion was approximately 35 min. One hour after discontinuing lidocaine, the pancuronium infusion was increased to produce a constant twitch depression of equal magnitude to that previously produced by the pancuronium–lidocaine combination. Edrophonium antagonism from this equal point of depression was again performed (*i.e.*, three 10 μg/kg doses over 1–1.5 min). In alternate animals the above order was reversed: edrophonium antagonism of the control pancuronium 70% twitch depression was assessed first; the pancuronium rate was then decreased to produce a stable 50% depression of twitch height; lidocaine was given by bolus and infusion as described above; and edrophonium antagonism of the combined block was assessed. In each animal, edrophonium antagonism of the neuromuscular blockade produced by the lidocaine and pancuronium combination was compared with antagonism of the blockade (of equal magnitude) produced solely by pancuronium. The significance of differences in antagonism of these two blockades was assessed by paired *t* test.

The interaction of verapamil and pancuronium was studied in the other five cats (fig. 2). A control twitch tension depression of 60% was established with pancuronium and antagonized with edrophonium (three 10 μg/kg doses over 1–1.5 min). One-half hour after the edrophonium was administered the pancuronium infusion rate was decreased to produce a stable 50% depression of twitch tension. Verapamil was then administered as a single intravenous bolus of 0.15 mg/kg, and the augmentation of twitch depression was recorded 5, 10, 20, and 30 min later. The significance of augmentation of blockade by verapamil was assessed by paired *t* test. Antagonism of the combined verapamil–pancuronium blockade was performed with edrophonium (at 30 min) and compared with the antagonism of the control pancuronium–induced neuromuscular blockade in each cat. The significance of differences in edrophonium antagonism of these two blockades was assessed by paired *t* test.

In each cat, pancuronium was discontinued at the end of the study and twitch tension allowed to return to baseline level. In two cats, lidocaine boluses (1.5 mg/kg and 1.0 mg/kg) and infusions (60 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were added after twitch height had returned to baseline to assess the effect of lidocaine on twitch tension in the situation where there was a subclinical concentration of pancuronium present at the neuromuscular junction.

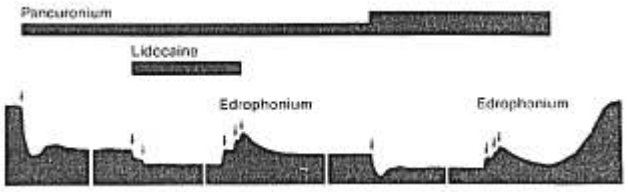

FIG. 1. The force of muscle contraction is shown for a typical lidocaine-pancuronium study. Proceeding from left to right, pancuronium was begun at the first *arrow* and continued as indicated by the *bar* above the graph. Lidocaine boluses were given at the second and third *arrows* and an infusion of lidocaine was begun as indicated by the *bar* above the graph. Note that lidocaine augments the pancuronium–induced blockade. Edrophonium was then administered in three sequential boluses (as indicated by the three *arrows*). The lidocaine infusion was stopped and at least 1 h passed before the pancuronium infusion was increased to produce a twitch tension depression equal to that produced by the lidocaine–pancuronium combination. Edrophonium was again administered in three sequential doses. The pancuronium infusion was then discontinued and the twitch tension allowed to recover to baseline.

Results

Lidocaine, when administered in the presence of subclinical pancuronium concentrations, had no effect on twitch height. The serum lidocaine levels averaged 5.09 μg/ml with a range of 3.36–8.02 despite identical boluses and infusion rates (in mg/kg). The addition of lidocaine during the pancuronium infusion increased the twitch depression 20.0 ± 5.5% ($P < 0.0001$) (table 1). The augmentation ranged from 11.5 to 30.8% and could not be

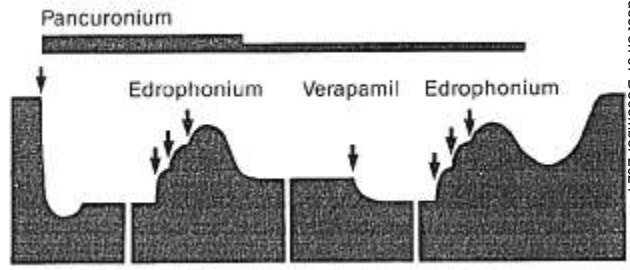

FIG. 2. The force of contraction is illustrated for a typical verapamil–pancuronium study. Pancuronium was begun at the first *arrow* and was infused at a constant rate to produce a 60% depression of twitch tension. Edrophonium was then administered in three sequential doses. The pancuronium infusion was decreased to produce a 50% depression of twitch tension. Verapamil was administered as a single bolus of 0.15 μg/kg. Note that verapamil augments the pancuronium–induced neuromuscular blockade. Edrophonium was again administered in three sequential doses. Pancuronium was discontinued and the twitch tension allowed to return to baseline.

TABLE 1. Lidocaine Augmentation of Pancuronium Neuromuscular Blockade

Cat	Pancuronium Infusion $\mu g \cdot kg^{-1} \cdot min^{-1}$	Per Cent Twitch Depression			Serum Lidocaine Level $\mu g/ml$
		Pancuronium Alone	Pancuronium plus Lidocaine	Augmentation with Lidocaine	
A	0.67	41.4	62.1	20.7	3.48
B	2.00	52.9	70.6	17.7	3.39
C	0.54	54.2	65.7	11.5	7.04
D	1.40	50.0	80.8	30.8	4.46
E	1.13	48.6	65.7	17.1	4.85
F	0.46	47.2	69.4	22.2	3.51
G	0.74	51.5	66.6	15.1	3.36
H	0.66	54.0	76.0	22.0	7.68
I	0.78	50.0	73.0	23.0	8.02
Average	0.93	50.0	70.0	20.0*	5.09

* $P < 0.0001$.

predicted on the basis of serum lidocaine levels (r = −0.01, fig. 3).

Administration of verapamil during the pancuronium infusion increased the twitch depression by 12.8 ± 8.0% (ranging from 4.7 to 26.2%; $P < 0.01$; table 2).

Edrophonium antagonized both the combined pancuronium–lidocaine (fig. 4) and pancuronium–verapamil (fig. 5) neuromuscular blockade to the same degree as the equivalent pancuronium–induced neuromuscular blockade. Lidocaine blood levels were stable during the edrophonium antagonism: levels measured before and after antagonism varied by a maximum of 14%.

Discussion

The interaction of neuromuscular blocking agents with lidocaine and verapamil has been reported to occur clinically. Administration of lidocaine, 3 mg/kg, in the presence of partial neuromuscular blockade was noted to produce a 7.5% depression of single twitch tension and a 40% decrease in tidal volume.[1] Similarly, difficulty antagonizing neuromuscular blockade in a patient treated with chronic verapamil infusions has been reported, and this difficulty was attributed to the neuromuscular blocking properties of verapamil.[2]

These clinical observations have been supported by laboratory reports. Lidocaine was reported to potentiate pancuronium's neuromuscular blocking activity in a rat phrenic nerve hemidiaphragm preparation.[3] However, the lidocaine concentration used (25 $\mu g/ml$) was at least four times the maximum therapeutic blood level in humans (*i.e.*, 5–6 $\mu g/ml$). Similarly, a 25% augmentation of *d*-tubocurarine twitch depression was observed when 5 mg/kg of lidocaine was given intravenously in cats.[4] Serum lidocaine levels were not measured, but this is three to five times the normal therapeutic dose for antiarrhythmia treatment in humans.

Verapamil has also been shown to produce neuromuscular blockade in animals. Lawson *et al.* reported that verapamil (0.1–1 mg/kg) produced a dose-related twitch

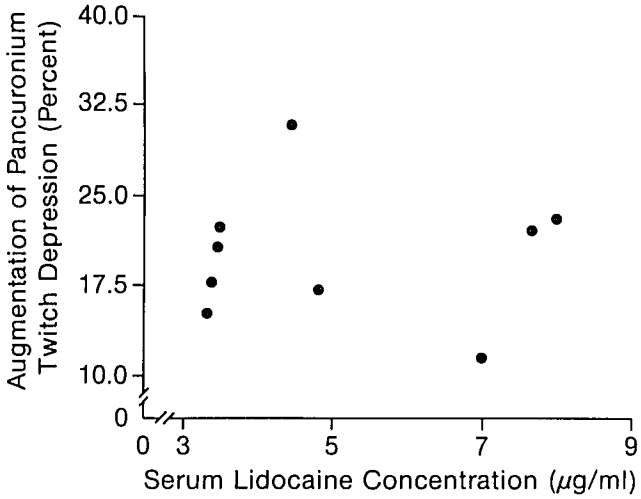

FIG. 3. When lidocaine was administered in the presence of a partial pancuronium neuromuscular blockade, the serum level of lidocaine did not correlate with the magnitude of the decrease in twitch tension (r = −0.01).

TABLE 2. Verapamil Augmentation of Pancuronium Neuromuscular Blockade

	Pancuronium Infusion $\mu g \cdot kg^{-1} \cdot min^{-1}$	Per Cent Twitch Depression		
		Pancuronium Alone	Pancuronium plus Verapamil 0.15 mg/kg	Augment by Verapamil
	0.74	50.0	61.3	11.3
	0.67	46.3	59.3	13.0
	0.46	47.6	73.8	26.2
	0.63	48.7	57.3	8.6
	0.73	52.4	57.1	4.7
Average	0.65	49.0	61.8	12.8*

* $P < 0.01$.

depression, ranging from 25 to 809, when administered to dogs.[6] Kraynack *et al.* observed a similar 20–80% reduction of twitch height after administering 0.1–0.4 mg/kg of verapamil to cats.[5]

Our study used lidocaine and verapamil doses similar to those used clinically in the treatment of cardiac arrhythmias in humans. Measured serum lidocaine concentrations confirmed that blood levels were in the therapeutic range for humans (table 1). The potency of lidocaine at the neuromuscular junction is likely to differ from species to species. The effect of lidocaine in humans may be equal, greater than, or less than what we observed in cats. Nonetheless, our results demonstrate that in cats lidocaine or verapamil infusions in these lower dose regimens can augment a partial pancuronium-induced neuromuscular blockade by up to 30%. Furthermore, the magnitude of augmentation could not be predicted on the basis of either the serum lidocaine level or the animals' sensitivity to pancuronium.

The mechanism of augmentation of neuromuscular blockade is unclear. Local anesthetics may theoretically interfere with every step involved in neuromuscular transmission. Lidocaine can completely block impulse conduction in the nerve and can also depress prejunctional and postjunctional impulse conduction.[7] Steinbach correlated the molecular structure of several lidocaine derivatives with their respective inhibition of neuromuscular transmission and their local anesthetic potency.[8] He found that the molecular properties of the lidocaine derivatives that are best correlated with the depression of neuromuscular transmission are not the properties associated with local anesthetic potency, but are molecular properties similar to those known to be important for acetylcholine activation of receptors. Steinbach's results imply that lidocaine produces neuromuscular block by a mechanism that is separable from its mechanism of local anesthetic action. Our results do not help to identify the specific sites of action of lidocaine. However, we do confirm the observation of Harrah *et al.* that lidocaine only exerts a measurable effect on neuromuscular function in the presence of partial neuromuscular blockade.[4]

The mechanism of action of verapamil is also unclear. Direct blockade of calcium channels in the muscle might be responsible for a decrease in twitch tension. However, the data of Lawson *et al.*[6] and Kraynack *et al.*[5] imply an

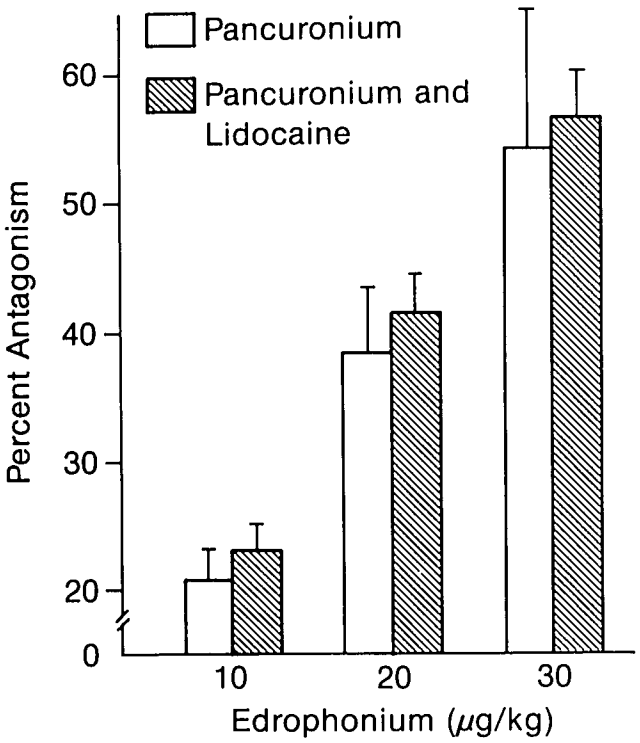

FIG. 4. Edrophonium antagonism of neuromuscular blockade produced by lidocaine and pancuronium is compared with antagonism of a pancuronium-induced blockade of equal magnitude.

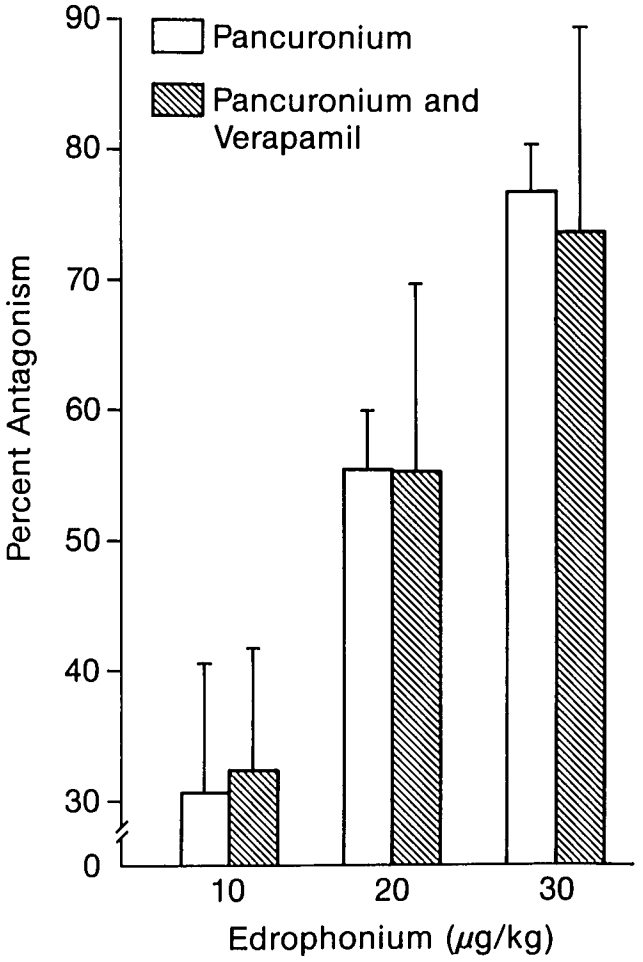

FIG. 5. Edrophonium antagonism of neuromuscular blockade produced by verapamil and pancuronium is compared with antagonism of a pancuronium-induced blockade of equal magnitude.

action of verapamil at the neuromuscular junction itself. This action on the nerve or nerve terminal is consistent with the observed local-anesthetic–like effect of verapamil. Further work is necessary to clarify the exact mechanism of action of verapamil's neuromuscular blocking property.

The reversibility of lidocaine- or verapamil-augmented neuromuscular blockade has not been previously quantitated. Matsuo *et al.* showed that 4-amino-pyridine was an adequate antagonist of lidocaine–pancuronium–induced neuromuscular blockade in an *in vitro* model,[3] but this agent is not available for use in humans. We studied low doses of edrophonium and found that regardless of the mechanism of augmentation, combined blockade with lidocaine or verapamil can be antagonized with edrophonium as easily as a similar degree of neuromuscular blockade produced by pancuronium infusion alone. Our results were obtained in the range of 60–75% depression of single twitch tension. We do not know how effective antagonism would be at the 90–99% range of twitch depression.

Our study design used each animal as its own control. This methodology has advantages as well as disadvantges. The major advantage is the elimination of interindividual differences in sensitivity of the neuromuscular junction. Cats, like humans, have a wide variability in sensitivity to drugs that effect neuromuscular transmission. Comparing the augmentation of neuromuscular blockade and the antagonism of neuromuscular blockade produced by the different drug regimens in the same animal eliminates the variability inherent in comparisons between different animals. However, sequential antagonism of neuromuscular blockade in the same animal introduces the potential for residual drug effects that may interfere with subsequent measurements. We feel that the interval between drug administrations was long enough to allow residual drug effects to dissipate. Edrophonium had transient effects that repeatedly were almost completely dissipated within 15 min, yet we had a minimum of 1 h between the administrations of this drug. Lidocaine, in contrast, probably was present in low concentrations at the time the pancuronium control was performed in the three animals where the lidocaine–pancuronium blockade was antagonized first. However, analysis of the ratios of the infusion rates of pancuronium required to produce the 50% and 70% neuromuscular blockade revealed no differences between the animals that received lidocaine before the pancuronium control and those that had the control performed first. In other words, there was no evidence of a residual lidocaine augmentation of blockade. All in all, we feel that the advantage of eliminating the variable sensitivity of individual animals was not offset by the potential for residual drug interactions.

In summary, we have found, in the cat, that doses of lidocaine in the therapeutic range for humans augment pancuronium–induced neuromuscular blockade by an average of 20%, and infusions of verapamil in the therapeutic range for humans augment blockade by 12.8%. This augmented blockade can be antagonized by edrophonium as easily as blockade produced by pancuronium alone. Although extrapolation to human responses may not be quantitatively similar, clinical implications are that neuromuscular blockade monitoring is appropriate in any patient receiving pancuronium in the presence of lidocaine or verapamil antiarrhythmic therapy, and that the doses of pancuronium may need to be reduced. If the degree of twitch depression is in the 50–75% range, antagonism with anticholinesterase agents may be expected to occur in a normal fashion.

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