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Potentiation of Neuromuscular Blockade by Verapamil

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The effects of intravenous (iv) verapamil (0.01 to 1.0 mg/kg) on the constant neuromuscular block produced by an iv infusion of either pancuronium or succinylcholine were studied on the indirectly stimulated gastrocnemius and tibialis-anterior muscles of the rabbit anesthetized with halothane in oxygen. Verapamil alone (n = 6) had no significant effect. However, the drug did significantly potentiate the 50% twitch depression of the gastrocnemius muscle produced by a constant iv infusion of either pancuronium (n = 5) or succinylcholine (n = 5) to 36 ± 6% and 45 ± 1% of control, respectively. This effect of verapamil occurred with doses of 0.1 mg/kg for pancuronium and 0.01 mg/kg for succinylcholine; these doses of verapamil were the lowest which produced a significant effect. In contrast, verapamil had no significant effect on the progression of the neuromuscular blockade of either the gastrocnemius or tibialis-anterior muscles produced by alpha-bungarotoxin (n = 5). Verapamil also significantly prolonged the P-R interval of the ECG from a control value of 71 ± 2 ms to 78 ± 3 ms at a dose of 0.1 mg/kg and to 93 ± 6 ms at a dose of 0.3 mg/kg. The possible mechanisms of the neuromuscular actions of verapamil are discussed and it is concluded that verapamil can produce potentiation of either pancuronium- or succinylcholine-induced neuromuscular block at doses within the therapeutic range. (Key words: Ions: calcium entry blockers, verapamil. Neuromuscular relaxants: pancuronium; succinylcholine. Pharmacology: alpha-bungarotoxin; verapamil.)

INTRAVENOUS VERAPAMIL (Isoptin®) was introduced into the United States in the fall of 1981 and is considered the drug of choice for treatment of supraventricular tachycardia. The mechanism of action of this drug is well-documented[1] and is due to blockade of the slow calcium ion influx into contractile and conductive myocardial cells which results in slowed conduction, prolonged refractory period and depression of contractility.[1]

The action of verapamil in myocardial cells has led to its use as a research tool for the investigation of the role of calcium in cardiac[2] and skeletal muscles.[3,4] Although the role of calcium in skeletal muscle is very different from cardiac muscle, the effects of verapamil on the indirectly elicited twitch tension in skeletal muscle have been observed following intra-arterial injection in cats[5] or *in vitro* using either the rat hemidiaphragm preparation[6] or the bullfrog sartorius muscle,[7] and recently following intravenous administration in the anesthetized cat[8] and dog.[9] Two of these studies[6,7] investigated and demonstrated the potentiation of nondepolarizing neuromuscular block by verapamil, which suggested that verapamil may potentiate neuromuscular block *in vivo*. However, none of these studies directly investigated the effects of verapamil on neuromuscular block *in vivo*. Recently, at our institution, a 17-year-old patient with Duchenne's dystrophy exhibited respiratory failure immediately following intravenous injection of verapamil.[10] This case indicated that verapamil may exacerbate muscle paralysis when neuromuscular transmission is compromised.

Thus, previous studies with verapamil and the above clinical case suggested that the effect of verapamil on neuromuscular block *in vivo* should be investigated. The present study was undertaken for two reasons: (1), to determine if verapamil does potentiate the neuromuscular block produced by either pancuronium or succinylcholine *in vivo;* and (2), to try to elucidate a possible site of action of verapamil on neuromuscular transmission.

Materials and Methods

Twenty-one male, New Zealand, white rabbits weighing between 2.9 and 3.8 kg were anesthetized with halothane in oxygen. Once anesthesia was induced and the trachea was intubated, the inspired halothane was decreased gradually to between 1 and 1.3% for maintenance of anesthesia during surgery and the rest of the experiment. The rabbits were ventilated artificially at a rate and tidal volume sufficient to keep the Pa_{CO_2}, Pa_{O_2}, and *p*H within normal limits. Esophageal temperature was maintained between 39° and 41° C.

The arterial blood pressure of each rabbit was recorded via a polyethylene cannula placed in a carotid artery and connected to a Beckman® transducer (type 4-327-0121); the arterial pressure also was used to trigger a Beckman 9857B cardiotachometer to record heart rate. The electrocardiogram (ECG) (lead II) was recorded using a Grass® 7P4F pre-amplifier and a Grass 79PCP polygraph run at a chart speed of 25 mm/s to measure the P-R interval of the ECG. Neuromuscular transmission was monitored by recording the twitch tension of the gastrocnemius and the tibialis-anterior muscles elicited by stimulation of the sciatic nerve with a square-wave pulse of 0.2-ms duration at supramaximal voltage and a frequency of 0.1 Hz, supplied by a Grass S88 stimulator and SIU5 isolation unit. The twitch tension was recorded via Grass FT10C force displacement transducers. In the experiments with pan-

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curonium, the electromyographic (EMG) response of the gastrocnemius muscle was recorded, using the method of Lee *et al.*[11] All recordings other than the ECG were made on a Beckman® R612 dynograph.

The rabbits were divided into four groups, each group received verapamil cumulatively over a dose range of 0.01 to 1 mg/kg (iv). Each dose was administered over a period of two minutes to avoid peripheral vasodilation and at intervals of 15 min. In the first group, the effects of verapamil alone (n = 6) were studied. In the second and third groups, pancuronium (n = 5) and succinylcholine (n = 5), respectively, were infused intravenously to achieve a constant, near 50% depression of the twitch tension of the indirectly stimulated gastrocnemius muscle; the effects of verapamil (same dosage protocol as for verapamil alone) on the steady-state neuromuscular block produced by the infusion of either succinylcholine or pancuronium were then studied. The fourth group (n = 5) of rabbits received incremental iv bolus doses of alpha-bungarotoxin (alpha-BTX) (total = 39–50 μg/kg, mean = 42 ± 2 μg/kg). The dose of alpha-BTX required to produce any depression of the twitch tension varied between rabbits, and consequently had to be titrated until depression was observed. Since the neuromuscular depression produced by this toxin progressed continually, it was not possible to study the effect of verapamil on a steady-state block, but rather on the slow rate of decline of twitch tension produced by alpha-BTX.

Drugs used were halothane (Halocarbon Laboratories), verapamil (Isoptin®, Knoll), succinylcholine (Anectine®, Burroughs-Wellcome), pancuronium (Pavulon®, Organon), and alpha-BTX (Miami Serpentarium). All drugs were dissolved in 0.9% saline and intravenously administered. All results are presented as the mean ± SEM. Differences between the effects of doses of verapamil in the same group were tested using the Wilcoxon signed rank test for matched pairs and between groups using the Mann-Whitney U-test, $P < 0.05$ being regarded as significant.

Results

Cardiovascular Effects

Comparison of the P-R interval of the ECG, the heart rate, and mean arterial blood pressure following verapamil when tested alone or in rabbits receiving an infusion of either pancuronium or succinylcholine did not reveal any significant difference in the response to the same cumulative dose of verapamil between groups using one-way analysis of variance. Accordingly, all data were pooled and are shown in figure 1. Verapamil caused significant changes in all the variables shown in figure 1, except for the mean arterial blood pressure at a dose of 0.01 mg/kg of verapamil.

Neuromuscular Effects

At any of the doses studied, verapamil alone did not produce any significant change in the twitch tension of either the indirectly stimulated gastrocnemius or tibialis-anterior muscles (see fig. 2). However, 30 min after the final dose of 1.0 mg/kg the twitch tension of the gastrocnemius muscle had decreased to 81 ± 10% of control.

An effect of verapamil was apparent when the twitch tension was decreased by a constant infusion of either pancuronium or succinylcholine (figs. 2 and 3). When the twitch tension of the indirectly stimulated gastrocnemius muscle was maintained at or as near to 50% of control twitch tension as possible (48 ± 2%) by an iv infusion of pancuronium (0.6 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), a dose-dependent potentiation of the neuromuscular blockade was observed, this effect was significant with doses of verapamil of 0.1 mg/kg and greater. The twitch tension of the tibialis-anterior muscle was significantly decreased by doses of verapamil of 0.3 mg/kg and above. At no time was there complete neuromuscular block and also there was no significant change in the depressed twitch tension of the gastrocnemius or tibialis-anterior muscles in the 30 min following the last dose of 1.0 mg/kg of verapamil. Qualitatively the response of the tibialis-anterior muscle to verapamil in the presence of pancuronium was very similar to that of the gastrocnemius muscle. The tibialis-anterior muscle was slightly more sensitive to pancuronium alone than the gastrocnemius muscle since the twitch tension was reduced to 40 ± 10% of control during the constant infusion of pancuronium compared with 48 ± 2% for the gastrocnemius muscle. In the experiments with pancuronium, the EMG and twitch tension of the gastrocnemius muscle were simultaneously measured. Regression analysis of these two variables indicated a significant correlation ($r = 0.6$, $P = 0.02$) following verapamil.

Succinylcholine-induced (21 ± 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) neuromuscular block also was potentiated in a manner similar to that of pancuronium (figs. 2 and 3). Verapamil significantly potentiated the succinylcholine-induced neuromuscular blockade of the gastrocnemius muscle at all doses tested; the tibialis-anterior muscle was similarly affected. There was evidence of a lack of further potentiation of the succinylcholine block with a dose of 1.0 mg/kg of verapamil on both muscles, particularly on the tibialis-anterior muscle, which exhibited an increase of twitch tension (fig. 2). Succinylcholine alone produced an almost identical depression of both the gastrocnemius (49 ± 1% of control) and tibialis-anterior (49 ± 4% of control) muscles.

In order to investigate the effect of verapamil on neuromuscular blockade produced by alpha-BTX, it was necessary to measure the rate of decline of twitch tension

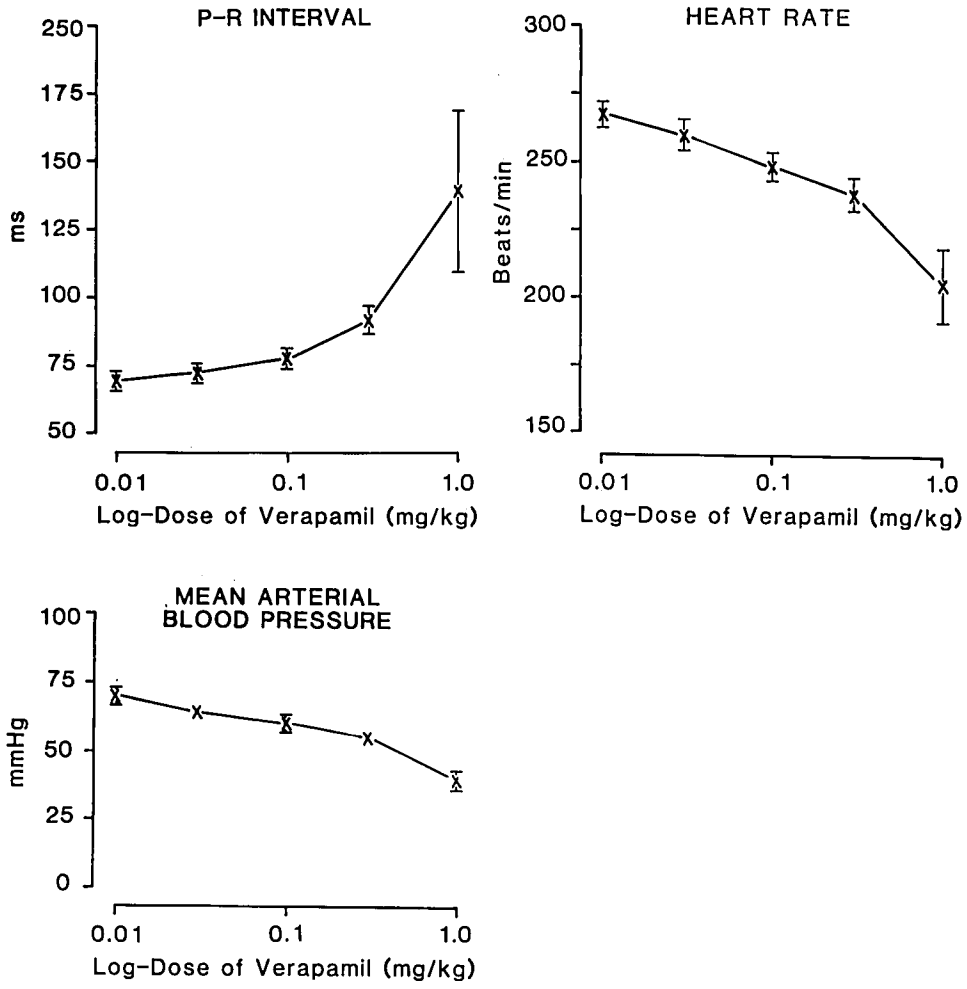

FIG. 1. The effect of verapamil on the P-R interval of the ECG, the mean arterial blood pressure and the heart rate. The graphs represent the pooled data (n = 16) from the experiments with verapamil alone or during an infusion of either pancuronium or succinylcholine. All effects are significantly ($P < 0.05$) different from control values, except for a dose of 0.01 mg/kg of verapamil on mean arterial blood pressure. The control value for the P-R interval is 71 ± 2 ms, the mean arterial blood pressure 72 ± 2 mmHg, and the heart rate 275 beats/min. The vertical bars indicate the SEM.

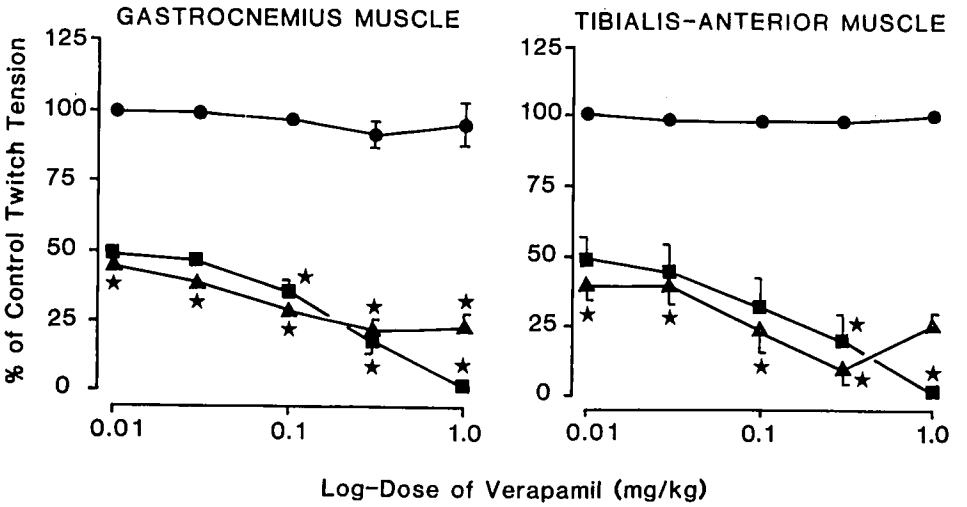

FIG. 2. The effect of verapamil on the twitch tension (expressed a percentage of control) of the indirectly stimulated gastrocnemius and tibialis-anterior muscles in untreated rabbits (●) and rabbits receiving an iv infusion of either pancuronium (■) or succinylcholine (▲). The twitch tension during the infusion of pancuronium for the gastrocnemius muscle was 52 ± 2% of control, and for the tibialis-anterior was 40 ± 10% of control before the verapamil. Similarly, during the infusion of succinylcholine, the twitch tension of the gastrocnemius muscle was 49 ± 1% of control, and the tibialis-anterior muscle was 50 ± 4% of control before the verapamil. The asterisk indicates a significant ($P < 0.05$) difference from twitch tension depression before the verapamil. The vertical bars indicate the SEM.

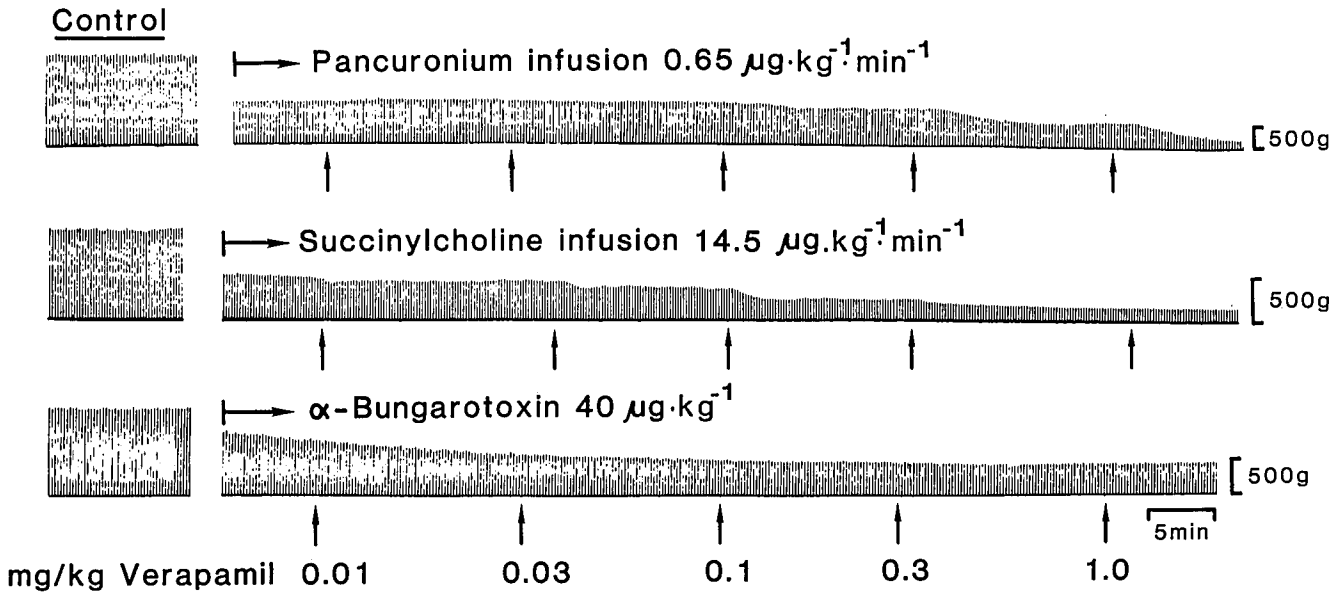

FIG. 3. Recordings from typical experiments that show the effect of verapamil on the twitch tension of the indirectly stimulated gastrocnemius muscle, during an intravenous infusion of pancuronium (*top*), succinylcholine (*middle*), or following a bolus dose of alpha-bungarotoxin (*bottom*).

following the toxin (42.2 ± 2 μg/kg) for the reasons previously described. Once the twitch tension of the gastrocnemius muscle had decreased to 75% of control then the cumulative administration of verapamil was started (see fig. 4). It was possible in only two rabbits to determine the rate of decline following 1.0 mg/kg of verapamil, and therefore these points are not included in figure 4. This figure illustrates that verapamil (0.01–0.3 mg/kg) had no significant effect on the rate of the decrease of twitch tension of the gastrocnemius or tibialis-anterior muscles following alpha-BTX.

Discussion

The present study clearly demonstrates that verapamil potentiates the neuromuscular block produced by either pancuronium or succinylcholine in the rabbit anesthetized with halothane, and thus confirms previous *in vitro* studies that show potentiation of nondepolarizing neuromuscular

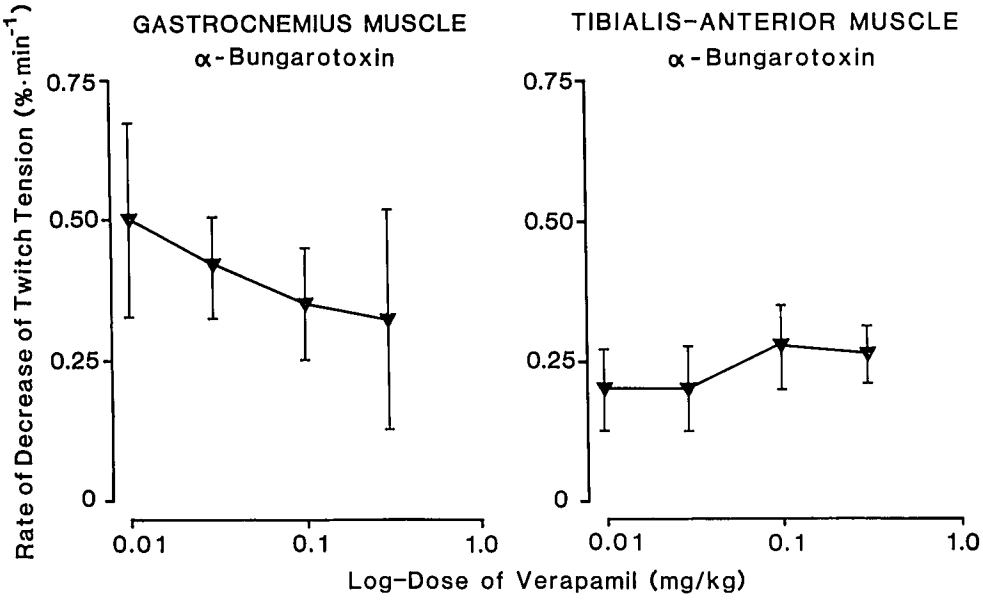

FIG. 4. The effect of verapamil on the rate of decline of the twitch tension of the indirectly stimulated gastrocnemius and tibialis-anterior produced by alpha-bugarotoxin. The rate of decline before verapamil of the gastrocnemius muscle was 0.55%/min, and for the tibialis-anterior muscle was 0.28%/min.

block by verapamil.[6,7] This effect of verapamil was observed at doses within the therapeutic range (0.1–0.3 mg/kg) and at doses that significantly prolong the P-R interval of the ECG, and thus also confirms that verapamil can affect neuromuscular transmission at clinically used doses. The prolongation of the ECG P-R interval observed with doses of verapamil of 0.1 and 0.3 mg/kg represents an increase of approximately 10 and 31%, respectively. These values are similar to that (40%) observed by Kapur and Flacke[12] using a dose of 0.2 mg/kg in anesthetized dogs.

That the action of verapamil is *not* centered on the muscle fiber itself is suggested by two observations: (1) no depression of twitch tension by verapamil alone was observed; and (2) in the experiments with pancuronium, the effects of verapamil on the depressed twitch tension and EMG exhibited an excellent correlation, consistent with an action on neuromuscular transmission. A preferential effect of verapamil on indirectly elicited twitch tension *vs.* directly elicited twitch tension has been reported by previous workers.[8]

A neuromuscular action of verapamil in the anesthetized rabbit appears to occur when the margin of safety is narrowed by pancuronium or succinylcholine but not by alpha-BTX; a neuromuscular effect of verapamil alone would not be expected because of the large margin of safety that exists at the neuromuscular junction. Waud and Waud[13] described the margin of safety of neuromuscular transmission as being 80–90% of all postjunctional receptors that must be blocked before there was any evidence of decreased twitch tension indirectly elicited at a frequency of stimulation of 0.1 Hz. Such an effect also could apply to impaired release, in that release of acetylcholine could be reduced to a large extent before transmission would be affected.

Why then is the neuromuscular block produced by alpha-BTX not significantly affected by verapamil? Although alpha-BTX produces nondepolarizing neuromuscular blockade, this action differs from the action of either pancuronium or succinylcholine in two significant additional ways, which suggests two possible explanations for the action of verapamil.

The first and possibly more plausible explanation lies in the differing abilities of the drugs tested to plug the post-junctional acetylcholine-activated ionic channels when they are open. Pancuronium but not alpha-BTX has been shown to block ionic conductance at the end-plate,[14] and results from unpublished experiments in our laboratory suggest that succinylcholine is similar to decamethonium[15] in that it also blocks the open acetylcholine-activated ionic channels. While at present there is no study that has directly investigated the effect of verapamil on the acetylcholine-activated ionic conductance of the end-plate, the methoxy-derivative of verapamil, D600, has been shown to possess the ability to block these channels when they are open.[16] Additionally, the local anesthetics are well-known to produce blockade of the open acetylcholine-activated ionic channel,[17] and verapamil has a local anesthetic potency which is 1.6 times that of procaine.[1] Thus, there is a large body of circumstantial evidence to suggest that verapamil may have an effect on the ionic conductance via the open acetylcholine-activated channels and that this effect may be responsible for the potentiation of pancuronium and succinylcholine but not alpha-BTX which acts only by receptor inactivation and lacks any direct action on endplate ionic conductance.[14] The likelihood of such an action of verapamil is supported by the observation of Chiarandini and Bentley[18] that verapamil blocks muscle contractions induced by acetylcholine in a noncompetitive manner in isolated toad skeletal muscle. This type of effect is consistent with an action of verapamil on the acetylcholine-activated ionic channels in the end-plate.

A second explanation may lie in the fact that pancuronium possesses a prejunctional depressant action[19,20] that may be manifested as both tetanic fade and train-of-four fade.[21] The prejunctional action of succinylcholine is more complex and involves an initial phase of increased transmitter release followed by depression.[22,23] In contrast, alpha-BTX exhibits very little affinity for a prejunctional binding site[19] and also, does not produce tetanic fade during depression of twitch tension.[24] Although verapamil has been shown to increase spontaneous acetylcholine release at the neuromuscular junction,[25] there unfortunately is little information available regarding evoked acetylcholine release. However, in terms of a local anesthetic action, verapamil, as suggested by Kraynack *et al.*,[8] might be expected to possess a depressant action, particularly as lidocaine has been shown to produce presynaptic depression.[20] The present results demonstrate that verapamil potentiates pancuronium and succinylcholine which possess a presynaptic depressant action at the neuromuscular junction; in contrast verapamil does not affect alpha-BTX which has no prejunctional effect.

In a recent study, Kraynack *et al.*[8] reported that iv verapamil alone (0.1–0.4 mg/kg) has a significant effect on twitch tension in the anesthetized cat and suggested that neuromuscular-blocking agents may be potentiated. The fact that, in contrast to Kraynack *et al.*,[8] we did not observe an effect of verapamil alone on twitch tension may be explained by a difference in species (cat *vs.* rabbit) and the method of anesthesia employed. However, we have demonstrated that neuromuscular-blocking agents are indeed potentiated by verapamil.

Two other observations are worthy of discussion: the sustained twitch depression in the pancuronium experiments and the reversal of succinylcholine-induced block by 1.0 mg/kg of verapamil on the tibialis-anterior muscle.

Kraynack *et al.*[8] reported an irreversible twitch depression with a slow onset in anesthetized cats similar to that observed in the present study with verapamil alone and pancuronium and verapamil; a similar irreversible effect of verapamil was reported *in vitro* by Bikhazi *et al.*[6] Kraynack *et al.*[8] postulate that this type of effect may be caused by the slow intracellular accumulation of verapamil and its metabolites in the skeletal muscle fibers.

The apparent reversal of the succinylcholine-induced depression of twitch tension by 1.0 mg/kg is hard to explain. Zaimis[26] demonstrated that the tibialis-anterior muscle of the anesthetized rabbit responded to decamethonium with tachyphylaxis and tetanic fade. If succinylcholine acts in the same manner, it is more than likely that the tibialis-anterior muscle of the rabbit does not respond to succinylcholine with a pure depolarizing block (*i.e.*, it tends towards a phase II-type block); this makes interpretation of the reversal of succinylcholine by 1.0 mg/kg of verapamil very difficult. However, our results clearly show that the depression of twitch tension produced by an infusion of succinylcholine is potentiated by verapamil within the clinical dose range.

It will be apparent from the above that two different possible explanations can be applied to explain the results of the present study. This dilemma is not confined to this study alone, but raises the question as to the relative roles of the pre- and postjunctional actions of different muscle relaxants and when these actions become important. It is not possible to say whether it is either of the above actions of verapamil that were responsible for the respiratory paralysis seen in the patient with Duchenne's dystrophy at our institution.[10] However, the fact that we observed potentiation of neuromuscular blockade at the same dose range as prolongation of the ECG P-R interval strongly suggests that neuromuscular effects of verapamil may be observed clinically, and particularly in patients with a compromised margin of safety of neuromuscular transmission.

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