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Comparison of Succinylcholine Induced Fasciculation Attenuation with Defasciculating Doses of Vecuronium and Mivacurium Based on Ideal Body Weight

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COMPARISON OF SUCCINYLCHOLINE INDUCED FASCICULATION ATTENUATION WITH DEFASCICULATING DOSES OF VECURONIUM AND MIVACURIUM BASED ON IDEAL BODY WEIGHT

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

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List of Abbreviations

Ach = Acetylcholine

ASA = American Society of Anesthesiologists

DMR = Depolarizing muscle relaxant

dTc = d-Tubocurarine

IBW = Ideal body weight

IV = Intravenous

kg = kilogram

mg = milligram

ml = milliliter

mSec = millisecond

Miv = Mivacurium

mV = millivolt

NMJ = Neuromuscular junction

NDMR = Nondepolarizing muscle relaxant

NMDRs = Nondepolarizing muscle relaxants

Sch = Succinylcholine

Vec = Vecuronium

Abstract

COMPARISON OF SUCCINYLCHOLINE INDUCED FASCICULATION ATTENUATION WITH DEFASCICULATING DOSES OF VECURONIUM AND MIVACURIUM BASED ON IDEAL BODY WEIGHT

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This study was conducted to determine if Mivacurium (Miv) was as effective as Vecuronium (Vec) in attenuating Succinylcholine (Sch)-induced fasciculations with muscle relaxant doses based upon ideal body weight (IBW). A quasi-experimental design was used to study 60 patients who were randomly assigned to one of three groups. The two study groups were compared to a control group and each other with regards to the incidence and intensity of fasciculations. Either Vec (0.01 mg/kg (IBW)), Miv (0.02 mg/kg (IBW)), or saline (control) was administered in a double-blinded manner 3 minutes prior an intubating dose of Sch (IBW). Both pretreatment modalities resulted in a significant ($p < .05$) decrease in the incidence (Vec 40%, Miv 60%) and intensity

of fasciculations when compared to saline (90%). No significant differences ($p > .05$) were found between the two pretreatment groups with regards to the incidence and intensity of fasciculations. It was concluded that Miv 0.02 mg/kg (IBW) attenuated Sch-induced fasciculations with the same efficacy as Vec 0.01 mg/kg (IBW).

Chapter One

Introduction

Since the introduction of neuromuscular blocking drugs into clinical anesthesia, the search for the ideal muscle relaxant has never ceased. Curare, a naturally occurring plant alkaloid, was discovered in the South American jungle where it was used by Amazonian indians as an arrow poison to paralyze their prey. It was the first neuromuscular blocking drug used as an adjunct to anesthesia by Griffith and Johnson (1942). Although curare opened a new era in modern anesthesia, it did not take long before disadvantages were recognized, two of which were the long duration of muscle relaxation and the release of histamine (Lee, 1984; Miller, 1989; Morgan & Mikhail, 1992; Scott & Savarese, 1984). Once these disadvantages were discovered the search began for the ideal muscle relaxant.

A multitude of drugs were synthesized in an attempt to produce muscle relaxation without detrimental side effects. One of these drugs was succinylcholine (Sch). Foldes (1952) introduced Sch into clinical anesthesia practice in the United States. One of the most important advantages of Sch

is its' rapid onset of action which is less than 1 minute. Even today, more than 41 years later, there is no muscle relaxant available with such a comparable onset of action (Lee, 1984; Miller & Savarese, 1990; Stoelting, 1991).

At the time of its clinical debut, Sch closely resembled the ideal muscle relaxant. It had a fast onset, a rapid and complete recovery, and a controllable intensity. Disadvantages were not easily recognized because most of the side effects were specific to Sch. Although the incidence and severity of complications following the use of Sch was high, it has retained its popularity because Sch remains the only muscle relaxant that provides excellent intubating conditions within 1 minute and complete recovery within 10 minutes (Bevan & Donati, 1985; Miller, 1989; Morgan & Mikhail, 1992).

Most of the serious side effects associated with Sch are a result of its effect on the myoneural junction. The list of side effects include: (1) muscle fasciculations, (2) postoperative myalgia, (3) increased intragastric pressure, (4) increased intracranial pressure, (5) increased intraocular pressure, and (6) hyperkalemia (Bevan & Donati, 1985; Lebowitz & Ramsey, 1989; Lee, 1984; Miller & Savarese, 1990; Stoelting & Miller, 1989). Several treatment regimes were employed to avoid these problems. They included the administration of small subparalytic doses of nondepolarizing muscle relaxants (NDMR) such as D-

tubocurarine, pancuronium, gallamine, atracurium, and vecuronium. Succinylcholine itself has also been used in small "self-taming" doses. Most of these regimes met with varying degrees of success in attenuating the fasciculations and postoperative myalgias (Bevan & Donati, 1985; Miller, 1989; Stoelting & Miller, 1989). Although there was not a clear relationship between the severity of the fasciculations and the intensity of the postoperative myalgias; the abolition of fasciculations by prior administration of a subparalytic dose of a NDMR decreased the incidence and severity of postoperative myalgias (Bevan & Donati, 1985; Lebowitz & Ramsey, 1989; Lee, 1984; Miller & Savarese, 1990; Stoelting, 1989). The efficacy of the NDMR in blocking fasciculations is related to its ability to inhibit the presynaptic action of Sch (Choi, Gergis, & Sokoll, 1985; Miller, 1989; Standaert, 1984).

Vecuronium, an intermediate acting NDMR, has been studied by several researchers as a defasciculating agent (Erkola, 1990; Ferres et al., 1983; Mingus, Herlich, & Esiencraft, 1990; Oshita et al., 1991). It has proven to be a safe and effective treatment modality for attenuating Sch-induced fasciculations. Vecuronium is a steroidal analog of pancuronium and because of its' rigid structure, it has predominantly postjunctional effects.

Mivacurium is the newest muscle relaxant used in anesthesia today. It is classified as a short-acting NDMR

with a duration of action between Sch and vecuronium. There has not been any published studies using mivacurium as a defasciculating agent. However, it may offer advantages over vecuronium in attenuating Sch-induced fasciculations. One possible advantage is mivacurium's potential of having prejunctional effects. Mivacurium's structure is flexible possibly allowing it more access to the prejunctional nicotinic cholinergic receptors (Miller & Savarese, 1990; Morgan & Mikhail, 1992; Stoelting 1989).

Purpose

The purpose of this study was to determine if mivacurium could be used with the same efficacy of vecuronium to prevent Sch-induced fasciculations with dosage regimes based on ideal body weight.

Research Questions

This study sought answers to 4 questions: (1) Can mivacurium (Miv) 0.02 mg/kg (ideal body weight (IBW)) given 3 minutes prior to the intravenous (IV) administration of Sch 1.5 mg/kg (IBW) prevent fasciculations in the face, upper torso, and upper extremities of ASA I and ASA II patients? (2) Can vecuronium (Vec) 0.01 mg/kg (IBW) given 3 minutes prior to the IV administration of Sch 1.5 mg/kg (IBW) prevent fasciculations in the face, upper torso, and upper extremities of ASA I and ASA II patients? (3) Can 2

ml normal saline solution given 3 minutes prior to the IV injection of Sch 1 mg/kg (IBW) prevent fasciculations in the face, upper torso, and upper extremities of ASA I and ASA II patients? (4) Is one of the three agents superior in preventing Sch induced fasciculations in the face, upper torso, or upper extremities of ASA I and ASA II patients?

Hypothesis

There is no significant difference in the attenuation of fasciculations in the face, upper torso, and upper extremities of ASA I and ASA II patients after the IV administration of Miv 0.02 mg/kg (IBW) or Vec 0.01 mg/kg (IBW) 3 minutes prior to Sch 1.5 mg/kg (IBW), or normal saline 2 ml 3 minutes prior to Sch 1.0 mg/kg (IBW).

Definition of Terms

ASA I. American Society of Anesthesiologists (ASA) class I patients are healthy and free of systemic diseases.

ASA II. ASA class II patients have mild to moderate systemic diseases but have no functional limitations.

Defasciculations. Defasciculation or precurarization is the IV administration of a subparalyzing dose of a NDMR to prevent fasciculations. The effectiveness is determined by the decrease in observable fasciculations.

Depolarizing muscle relaxant. A depolarizing muscle relaxant (DMR) mimics the action of acetylcholine (Ach),

producing depolarization of the postjunctional membrane. The metabolism of a DMR is slow compared to Ach, resulting in sustained depolarization. Skeletal muscle paralysis occurs because a depolarized neuromuscular junction (NMJ) can not respond to subsequent release of Ach.

Fasciculations. Fasciculations are transient generalized skeletal muscle contractions. The presence and degree of fasciculations were rated on a 0 to 3 scale. A score of 0 equaled no observable fasciculations. Very fine muscular movements of the eyelids, face and finger tips were classified as level 1 fasciculations. Level 2 fasciculations were classified as minimal muscular movements of the face, chest and upper extremities. A classification of 3 was demonstrated by muscular contractions which caused limb and head movement.

Ideal Body Weight. The ideal body weight (IBW) is the "ideal" weight for a person based on height and body frame size which is derived from actual tables. One calculation of IBW is: IBW (in kilograms (kg)) = a person's height (in inches) x 2.5 - 100. For example, a person that weighs 110 kg and is 67 inches (in) tall has an IBW of 67.5 kg (IBW (kg) = 67 (in) x 2.5 - 100).

Latency period. The latency period is that amount of time allowed to elapse between the administration of drug and its onset of action. The latency period for NDMR is 3 minutes when used as a defasciculating agent.

Mivacurium. Mivacurium is the newest NDMR. Metabolism occurs by pseudocholinesterase, but at a rate slower than Sch.

Nondepolarizing muscle relaxants. Nondepolarizing muscle relaxants compete with acetylcholine for binding sites in the NMJ and prevent changes in the permeability of the postjunctional membrane. As a result, depolarization cannot occur and skeletal muscle paralysis ensues. Skeletal muscle fasciculations do not occur with NDMR.

Succinylcholine. Succinylcholine is a depolarizing muscle relaxant. Its onset of action is within 1 minute with complete recovery in 10 minutes. The usual dose of Sch is 1 mg/kg. However, when a NDMR is used for defasciculation, the Sch dose is increased to 1.5 mg/kg.

Vecuronium. Vecuronium is a NDMR of intermediate duration. It is a monoquarternary steroidal analogue of pancuronium.

Variables

Independent. The independent variables are Miv 0.02 mg/kg (IBW), Vec 0.01 mg/kg (IBW) (3 minutes prior to Sch 1.5 mg/kg (IBW)), and normal saline solution 2 ml (3 minutes prior to Sch 1 mg/kg (IBW)).

Dependent. The dependent variable is the occurrence of observable muscle fasciculations of the face, upper torso, and upper extremities.

Limitations

1. An individual's response to a nondepolarizing muscle relaxant varies.

2. An individual's response to a depolarizing muscle relaxant varies.

3. Fasciculations may be too fine and/or too brief to be observed.

4. Parturients, children, ASA III, and ASA IV patients are excluded from participation in this study.

Delimitations

1. A blinded observer accurately recorded fasciculations based on a 0 to 3 rating scale.

2. All subjects were randomly assigned to one of three treatment groups: a control group or one of two experimental groups. Assignments were based on a table of random numbers in a double-blinded fashion.

3. For patient safety, all subjects with known sensitivities to any drugs used in this study were excluded.

4. All subjects between the ages of 18 years and 75 years with no significant neuromuscular, cardiac, hepatic, or renal disease were considered for possible inclusion to this study.

5. All subjects were classified as ASA I or ASA II and having surgical procedures requiring general anesthesia with endotracheal intubation.

Assumptions

1. Medications given preoperatively and for induction of general anesthesia did not affect neuromuscular transmission.

2. The latency period of 3 minutes was adequate for onset of action of the NDMR and was strictly adhered in all subjects.

3. Observers accurately recorded muscle fasciculations based on a 0 to 3 rating scale.

4. Various induction drugs and techniques did not affect fasciculations.

5. Muscle fasciculations were a common side effect of Sch administration.

6. Muscle fasciculations were not a typical side effect of NDMR.

7. Muscle relaxants were administered based on IBW.

8. The Brocca index, a formula for calculating IBW, was consistent in determining IBW for all subjects based on their height.

9. The primary anesthetist correctly administered saline, Miv, Vec, and Sch as dictated by the number assigned each respective subject.

Conceptual Framework

Neuromuscular junction. The neuromuscular junction is formed by a prejunctional motor nerve ending that is

separated from a postjunctional membrane of the skeletal muscle by a synaptic cleft (see Figure 1).

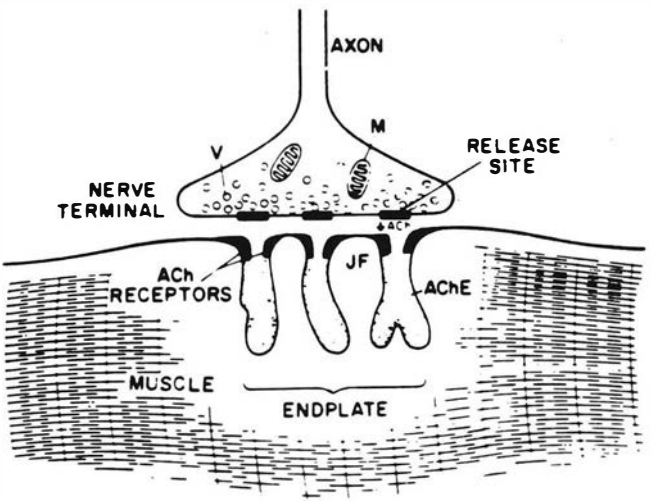

Figure 1. Schematic representation of the neuromuscular junction. Note. From Basics of Anesthesia (2nd ed) (p. 93) by R. K. Stoelting and R. D. Miller, 1989, New York: Churchill Livingstone.

The initiation of a neuromuscular transmission is caused by the arrival of a nerve impulse at the motor nerve terminal that results in an influx of calcium. This influx of calcium stimulates the neurotransmitter acetylcholine to be released. Once released, Ach binds to the postjunctional nicotinic receptors altering the permeability of the

postjunctional membrane to potassium and sodium. This ionic flux and change in permeability results in a decrease in the transmembrane resting potential to threshold potential (-90 mV to -45 mV). Once the threshold potential is achieved, the action potential is propagated over the surface of the muscle fibers resulting in muscular contraction. Acetylcholine is metabolized within 15 mSec by acetylcholinesterase, thereby restoring resting membrane potential and permeability and preventing sustained muscular contraction. Acetylcholinesterase is located in the folds of the postjunctional membrane.

Nicotinic cholinergic receptors are the most important sites of action of muscle relaxants. These receptors are located both prejunctionally and postjunctionally. The prejunctional receptors influence the release of acetylcholine. The postjunctional receptors are located exactly opposite the prejunctional receptors. The postjunctional receptors are large glycoproteins. Each receptor consists of 5 protein subunits, 2 alpha, 1 each of beta, delta, and gamma. These subunits are arranged in such a way that a channel is formed allowing the ionic flux of potassium and sodium to occur across the cell membrane (see Figure 2).

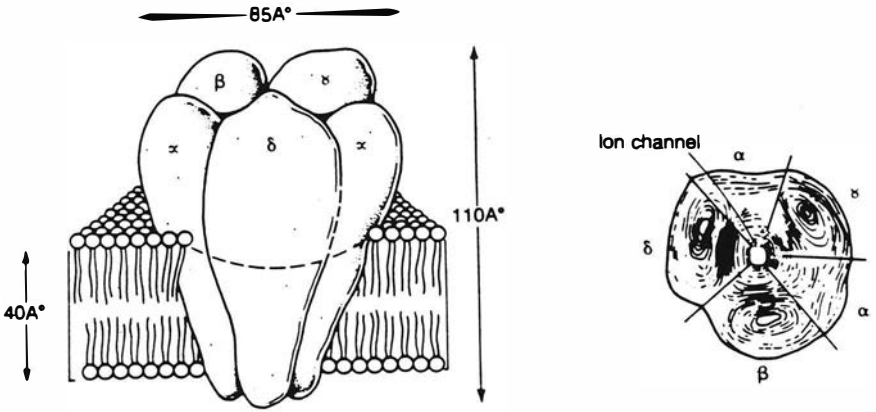

Figure 2. Postjunctional nicotinic cholinergic receptors. Note. From Basics of Anesthesia (2nd ed) (p. 93) by R. K. Stoelting and R. D. Miller, 1989, New York: Churchill Livingstone.

The two alpha subunits are the binding sites for Ach and muscle relaxants. For example, Sch mimics Ach when it is bound to the alpha subunits and permits the ion channel to remain open. However, because Sch is metabolized slower than Ach there is prolonged depolarization. Occupation of the alpha subunits by a NDMR causes the channel to remain closed, thus muscular contraction cannot occur. Large

overdosages of NDMRs can also plug the channel and prevent normal ionic flux from occurring.

Skeletal muscle fasciculations. The origin of Sch induced skeletal muscle fasciculations has been the source of controversy for many years. It was originally believed to be the result of asynchronous depolarization of the postsynaptic membrane of individual muscle cells by Sch. This explanation is unacceptable for three reasons: 1) the asynchronous depolarization of individual muscle cells are not observable externally, 2) entire motor units (300-2000 muscle cells) are activated simultaneously, and 3) fasciculations occur repeatedly in the same area of the muscle. Over the past 3 decades, accumulation of pharmacologic information suggests that nondepolarizing and depolarizing muscle relaxants have many sites of action at the NMJ. The efficacy of a NDMR in blocking Sch-induced fasciculations is related to its ability to inhibit the presynaptic action of Sch (Choi, Gergis, & Sokoll, 1985; Lebowitz & Ramsey, 1989; Miller & Savarese, 1990; Stoelting & Miller, 1989).

Depolarizing muscle relaxants. Depolarizing muscle relaxants mimic Ach. That is, they bind to the alpha subunits of the cholinergic receptor. However, the metabolism of depolarizing muscle relaxants is very long compared to the metabolism of Ach. The resulting depolarization of the postsynaptic membrane permits a

prolonged ionic flux that prevents repolarization of the muscle membrane from occurring. Without repolarization, the muscle membrane is unable to respond to further releases of Ach and muscle relaxation continues for several minutes (Lebowitz & Ramsey, 1989; Miller, 1989; Miller & Savarese, 1990; Stoelting, 1991; Stoelting & Miller, 1989).

Nondepolarizing muscle relaxants. Nondepolarizing muscle relaxants compete with Ach for the alpha subunits binding sites of the cholinergic receptor. Once bound, NDMRs alter the permeability of the ion channel preventing the ionic flux. Depolarization of the muscle membrane is prevented and the muscle remains flaccid. Skeletal muscle contraction cannot occur until the NDMR unbinds from the alpha subunits and diffuses away from the receptor site. This vacant receptor site is now available to bind with Ach to permit the ionic flux and depolarization to reoccur (Lebowitz & Ramsey, 1989; Miller, 1989; Stoelting & Miller, 1989).

The rationale for administering a defasciculating dose of a NDMR is to prevent fasciculations from occurring by occupying the alpha receptors on the presynaptic cholinergic receptor. The efficacy of NDMR preventing Sch induced fasciculations depends on its ability to block the presynaptic effect of Sch (Lebowitz & Ramsey, 1989; Miller & Savarese, 1990).

Administration of muscle relaxants based on ideal body weight. Muscle relaxants are highly ionized at physiologic pH and possess limited lipid solubility. Because of their hydrophilic nature, the volume of distribution is small, being limited to the extracellular fluid. As a result of this hydrophilicity, muscle relaxant dosages should be calculated on IBW instead of actual body weight (Cheymol, 1988).

Muscle relaxants do not cross lipid membranes because they possess at least one positively charged ammonium group and are usually large molecules. However, the large aqueous pores in the systemic vasculature allow the muscle relaxants access to the neuromuscular junction where they readily bind to the cholinergic receptors (Guyton, 1991; Stoelting, 1991).

To prevent muscle relaxant overdoses the IBW should be used because it more closely correlates to the lean body weight. The actual body weight has two components, lean weight and fatty weight. Doses of hydrophilic drugs (i.e., muscle relaxants) calculated on actual body weight are actually overdoses because they do not cross lipophilic membranes (i.e., fatty tissue) (Cheymol, 1988).

Overdosing with a defasciculating dose of a NDMR can result in apnea, partial paralysis, and patient anxiety. A Sch overdose results in an increase in the intensity of muscular fasciculations and a prolonged muscle paralysis

(Bevan & Donati, 1985; Miller & Savarese, 1990; Stoelting, 1991).

Summary

It has become standard practice to use defasciculating doses of NDMR to prevent Sch-induced fasciculations. The efficacy of these doses is related to their ability to block the presynaptic effect of Sch. Also, the use of IBW to calculate the doses of muscle relaxants prevents overdosing of these drugs.

Vecuronium was chosen for this study for 3 reasons. First, Vec is frequently used to provide muscle relaxation during general anesthesia. Secondly, it has proven itself to be a safe and effective agent in preventing Sch-induced fasciculations. Lastly, because of its' rigid structure, it has predominantly postjunctional effects. Mivacurium was selected because there are no published studies on its' use as a defasciculating agent. Also, it has the potential for an enhanced prejunctional effect when compared to Vec.

Chapter Two

Review of the Literature

Muscle Fasciculations

There has been considerable controversy over the origin of Sch-induced fasciculations. It was originally believed to be the result of Sch-induced asynchronous depolarization of the postsynaptic membrane of individual cells (Choi, Gergis, & Sokol, 1985). Others believed that depolarization of the muscle endplate led to local action potentials that spread to adjacent membranes, causing uncoordinated muscular contractions (Dripps, Eckenhoff, & Vandam, 1982).

Over the past 3 decades there have been an accumulation of pharmacological data that suggest cholinergic agonists have actions on the postsynaptic neuromuscular junction and on the prejunctional nerve terminal itself. Riker (1975), and Standaert and Adams (1965) demonstrated the presence of cholinergic receptors both pre- and postjunctionally. Their research suggested the origin of Sch-induced fasciculations was the result of prejunctional cholinergic receptor activation. Hartman, Flamengo, and Riker (1986) found the prejunctional receptors influenced the release of Ach. They

demonstrated a feedback mechanism in which cholinergic agonists caused an increase in the release of Ach and antagonists decreased or blocked it's release. These actions were demonstrated when Sch, an agonist, was given and produced fasciculations, and when d-tubocurarine, an antagonist, was given as a pretreatment and fasciculations were prevented.

Fasciculations can be described as the synchronized contractions of all muscle cells in a motor unit which are produced by the stimulation of the prejunctional cholinergic receptors of a motor nerve terminal. It has been demonstrated repeatedly that Sch-induced fasciculations and their attenuation occur because depolarizing and nondepolarizing muscle relaxants act directly on motor nerve terminals. The clinical significance of fasciculations is their proposed relationship to the occurrence of postoperative myalgias and increased intraocular and intragastric pressures (Standaert & Riker, 1967).

Vecuronium

Vecuronium is a monoquaternary analog of the steroid muscle relaxant pancuronium. It is an intermediate acting NDMR with excellent cardiovascular stability and does not cause the release of histamine. It is metabolized in the liver and excreted in bile. Muscle relaxation is obtainable with smaller doses than gallamine, dTc, or metocurine. The

onset of action of Vec is 3 minutes with a duration of 25 to 40 minutes (Miller, 1984).

Mivacurium

Mivacurium is a benzylisoquinoline derivative. It is the newest of the NDMRs. Mivacurium is a short acting NDMR with an onset time of 2.5 to 3 minutes and a duration of 20 to 30 minutes. It does cause the release of histamine but to a much less degree than dTc. Metabolism occurs from the enzyme pseudocholinesterase and minimally by true cholinesterase (Morgan & Mikhail, 1992).

Previous Studies on the Use of NDMRs as Pretreatments

Gallamine. Churchill-Davidson (1954) was the first to associate postoperative myalgia with Sch-induced fasciculations. He attempted to correlate the severity of the postoperative myalgia with the intensity of the fasciculations. There were 3 groups in this study. Group I (n = 32) were outpatients. Group II (n = 36) were inpatients confined to bed for 48 hours postoperatively. Group III (n = 15) were also outpatients. Groups I and II received Sch for muscle relaxation without any pretreatment. Group III received gallamine 40 mg immediately before Sch.

Demographic data was similar between all groups. Groups I and II had a 100% incidence of fasciculations and a 66% and 13.9% incidence of postoperative myalgia,

respectively. Group III had no visible fasciculations but a 40% incidence of postoperative myalgia. Churchill-Davidson concluded that if Sch is used for muscle relaxation during outpatient procedures, it should be preceded by gallamine 40 mg. He also concluded that the abolition of fasciculations reduced the incidence and severity of postoperative myalgia.

This classic study sparked interest in using NDMRs as pretreatments in preventing Sch-induced fasciculations. Burtles and Tunstall (1961) reduced the gallamine dose from 40 mg to 8 mg and compared it with 5 mg of Sch. The 174 patients studied were divided into three groups. Group I (n = 61) received normal saline prior to Sch. Group II (n = 56) received 5 mg Sch prior to a full relaxing dose of Sch. Group III (n = 57) received gallamine 8 mg prior to Sch. Group I (saline group) served as controls. The authors used a blinded methodology for this study.

The incidence of fasciculations in Group I was 82%, Group II 68%, and Group III 31%. The reduction of fasciculations in Group III was significant ($p < .01$). One error of the study the researchers identified was the failure to control the time interval between the pretreatment and the administration of Sch. The time interval they attempted to adhere to was 3 minutes; however, they acknowledged that at times it was shorter or longer.

Masey, Glazebrook, and Goat (1983) essentially duplicated Burtles and Tunstall's research, however, they

doubled the gallamine and Sch doses. Fifty patients were randomly divided into two groups. Group I (n = 25) received Sch 10 mg 1 minute before Sch 1 mg/kg. Group II (n = 25) received gallamine 20 mg 3 minutes prior to an intubating dose of Sch (1 mg/kg).

Fasciculations occurred in 20% of Group II and 80% of Group I. The authors concluded that pretreatment with Sch was ineffective in preventing fasciculations. They also stated that though gallamine significantly reduced fasciculations, intubation conditions were not as satisfactory as with no pretreatment. The authors used Sch 1 mg/kg as an intubating dose after the pretreatment with gallamine. They concluded the dose of Sch should be 1.5 mg/kg after a NDMR is used for pretreatment.

d-Tubocurarine. As interest increased in the relationship of Sch-induced fasciculations and postoperative myalgias, other NDMRs were studied in attempts to decrease both. A popular NDMR of the time was d-tubocurarine (dTc). Lamoreaux, Karl, and Urbach (1960) divided 113 male patients into 4 groups. Group I (n = 25) received Sch 50 mg as a single bolus. Group II (n = 20) received dTc 3 mg prior to Sch 50 mg. Group III (n = 35) received Sch 0.2% solution by slow infusion. Group IV (n = 33) received dTc 3 mg prior to Sch 0.2% solution by slow infusion.

Fasciculations only occurred in Group I. Postoperative myalgia occurred in 40% of patients in Group I, 14% in Group

III, and 18% in Group IV. There were no postoperative myalgias reported in Group II. They concluded that the speed of injection and concentration of Sch contributed to the occurrence of fasciculations and the incidence of postoperative myalgia. Their results failed to demonstrate a correlation between the severity of muscular fasciculations and the development of postoperative myalgia.

Another study employing dTc for defasciculation was performed by Bennike and Nielsen (1964). Three hundred patients were divided into 3 groups. Group I (n = 100) patients were anesthetized without relaxants. This group was included to study the incidence of postoperative myalgia in patients who received no muscle relaxants. Group II (n = 100) received Sch 50-100 mg as a single dose, rapidly injected. Group III (n = 100) received dTc 2 to 4 mg 2 minutes prior to Sch 50-100 mg. The dTc was adapted to body weight, i.e., approximately 0.05 mg/kg. Fasciculations were assessed as mild (few fasciculations), moderate (generalized fasciculations), or severe (so pronounced as to cause movement of the shoulders and limbs).

As expected, no fasciculations occurred in Group I. Group II had a 65% incidence of fasciculations with 26% being mild, 33% being moderate, and 6% being severe. In Group III, fasciculations occurred 14% of the time, with 11% being mild and 3% being moderate. Again, there was no simple correlation between the intensity of fasciculations

and the severity of postoperative myalgia, as some patients, who had no visible fasciculations developed postoperative myalgia and vice versa. However, there was a decrease in the occurrence of fasciculations and a decreased incidence of postoperative myalgia in the group that received dTc as a pretreatment.

In 1967 Zhorov, Michelson, Krochaler and Sevadjian investigated the prophylactic value of a defasciculating dose of 3 NDMRs and neostigmine. The patients were divided into 3 groups of 50. Group I patients were given dTc 3-5 mg, diplacin 10-15 mg, or kvalidil 10-15 mg as defasciculation doses. Diplacin and kvalidil are nondepolarizing muscle relaxants used in the Soviet Union. Sch 120 mg was injected 60-80 seconds after the pretreatment. Group II patients did not receive any pretreatment but were given neostigmine 0.5-0.75 mg intramuscularly 20-30 minutes preoperatively. Group III patients served as controls and did not receive a NDMR pretreatment or neostigmine.

Fasciculations were most prevalent in the control group. They occurred in 86% of the patients. Group II had similar results in that fasciculations occurred 82% of the time. The incidence of fasciculations was the least in group I patients.

The authors' data demonstrated a consistent finding compared to previous studies. The group that received the

defasciculating dose of a NDMR had fewer and less intense fasciculations and the occurrence and severity of postoperative myalgia was reduced.

Manchikanti (1984) compared dTc to diazepam for pretreatment in preventing fasciculations and myalgia. He randomly assigned 587 patients to 6 groups. Group I (n = 99) patients received no pretreatment and served as controls. Sch 1.0 mg/kg was given for muscle relaxation. Group II (n = 131) received diazepam 0.05 mg/kg 4-5 minutes prior to Sch 1.0 mg/kg. Group III (n = 71) received diazepam 0.05 mg/kg 8-10 minutes prior to Sch 1.0 mg/kg. Group IV (n = 97) received diazepam 0.1 mg/kg 4-5 minutes prior to Sch 1.0 mg/kg. Group V (n = 93) received diazepam 0.1 mg/kg, 8-10 minutes prior to Sch 1.0 mg/kg. Group VI (n = 96) received dTc 0.05 mg/kg, 4-5 minutes prior to Sch 1.5 mg/kg. Fasciculations were graded on a four point scale where 0 = no fasciculations, 1 = just visible fasciculations, 2 = moderate contractions, and 3 = vigorous contractions.

Fasciculations were seen in 90% of patients in the control group. The frequency and intensity of fasciculations were unaltered by pretreatment with diazepam in both dose ranges and different time intervals in Groups II through V. D-tubocurarine was highly effective (p = .0000001) in diminishing the frequency from 90% to 15% and vigorous contractions from 31% to 1%.

This study demonstrated that prior administration of diazepam 0.05 mg/kg or 0.1 mg/kg given either 4-5 or 8-10 minutes prior to Sch was ineffective in altering the frequency of intensity of fasciculations. It also indicated that pretreatment with dTc was highly effective in diminishing the frequency and intensity of fasciculations. The author concluded that defasciculating with dTc was superior to pretreatment with diazepam and should be the method of choice for prevention of Sch-induced fasciculations.

Pancuronium. By the early 1970s, pancuronium had entered the clinical anesthetic arena as the newest NDMR. At the same time, concerns surfaced that pretreatments with NDMRs increased the difficulty of tracheal intubation by antagonizing Sch depolarization. Cullen (1971) studied 158 patients to determine the combination of drugs, dose, and time interval that would attenuate Sch-induced fasciculations but retain excellent conditions for tracheal intubation. In this study, 158 male and female patients (ASA I or IE) were divided into 13 groups. Sch was studied at two dosage levels of 1 and 1.5 mg/kg alone and in combination with dTc (1.5 and 3 mg), pancuronium (0.5 and 1 mg), or gallamine (5, 10, 20, and 40 mg). The pretreatment regimes were studied at two time intervals of 3 and 7 minutes prior to Sch.

Fasciculations were graded on a 4 point scale where 0 = no visible fasciculations, 1 = very fine finger tip movements, 2 = minimal contractions of the trunk and extremities, and 3 = vigorous contractions of the trunk and extremities. Degrees of relaxation were also assessed using tracheal intubation as a stimulus. Muscle relaxation was graded on a 4 point scale where 3 = complete relaxation with no muscular response to intubation, 2 = slight coughing movements associated with contraction of the diaphragm, 1 = vigorous coughing with contractions of the diaphragm and trunk muscles, and 0 = relaxation was so inadequate that intubation was impossible.

As could be expected with 13 treatment groups, a large amount of data was collected. A summary of the findings followed. The control group had vigorous fasciculations, but muscle relaxation was complete. Gallamine 10-20 mg 3 minutes prior to Sch 1.5 mg/kg both abolished fasciculations and retained excellent intubating conditions. D-tubocurarine 3 mg 3 minutes prior to Sch 1.5 mg/kg provided adequate intubating conditions but fasciculations occurred in 40% of patients. When Sch 1 mg/kg was preceded by gallamine or dTc, relaxation was inadequate, confirming the need to increase the Sch dose by 50% when pretreating with a NDMR. Pretreatment with pancuronium was unsatisfactory because patients either had fasciculations or were inadequately relaxed. This study confirmed that intubating

difficulties did occur when gallamine or dTc preceded Sch 1 mg/kg. However, the author found that increasing the Sch dosage to 1.5 mg and pretreating with gallamine rather than dTc or pancuronium, prevented fasciculations while allowing rapid onset of excellent intubating conditions. The author recommended gallamine 10-20 mg 3 minutes prior to Sch 1.5 mg as the best pretreatment regime.

Wig and Bali (1979) conducted a study that was aimed at finding the best dose combination based upon a body weight basis of Sch with dTc, gallamine, and pancuronium as pretreatments. Ease of tracheal intubation, visible muscle fasciculations, and postoperative myalgias were assessed. The authors were blinded until completion of the study.

Two hundred and ten ASA Class I adults were divided into 21 groups of 10 patients each. No premedication was given to permit better assessment of intubating conditions and postoperative myalgias. Sch was investigated at three dosage levels of 1, 1.5, and 2.0 mg/kg alone as controls, or in combination with dTc (0.05 and 0.07 mg/kg), gallamine (0.2 and 0.4 mg/kg), or pancuronium (0.01 and 0.02 mg/kg), All pretreatment regimes were administered 3 minutes prior to Sch. Induction of anesthesia was standardized with thiopentone 5 mg/kg. Intubation was attempted 45 seconds after the Sch injection and intubating conditions were assessed. Visible muscle fasciculations were graded as absent, mild, moderate, or severe. Data about postoperative

myalgias were obtained 6, 24, and 48 hours using a questionnaire instrument.

Patients in the three control groups had mild to severe muscle fasciculations but pretreatment with NDMRs reduced the incidence significantly. Both doses of dTc significantly reduced the incidence of fasciculations to 10% and 20%, respectively ($p = < .0001$, and $< .01$). Only one group in the gallamine series (gallamine 0.2 mg/kg 3 minutes prior to Sch 1.5 mg/kg) had a 10% incidence of moderate fasciculations ($p = < .001$). Pancuronium at 0.01 mg/kg was much less effective that dTc, gallamine, or pancuronium 0.02 mg/kg in preventing fasciculations. As the dose of Sch was increased, the incidence of fasciculations rose from 10 to 100%. Pancuronium 0.02 mg/kg completely prevented visible muscle fasciculations.

Intubating conditions were best (100% success rate) when Sch was used alone at the 2 mg/kg level. Pretreatment with NDMRs resulted in a higher incidence of difficult tracheal intubations. Ideal conditions were achieved only when Sch 2 mg/kg was administered in combinations with dTc 0.07 mg/kg ($p < .1$), gallamine 0.2 mg/kg ($p < .1$), and pancuronium 0.02 mg/kg ($p < .01$). Intubation conditions were inadequate when the Sch dose was kept at 1.0 or 1.5 mg/kg after pretreatment with dTc 0.05 mg/kg and 0.07 mg/kg ($p < .01$), gallamine 0.2 mg/kg and 0.4 mg/kg ($p < .01$), and pancuronium 0.01 mg/kg and 0.02 mg/kg ($p < .01$).

The authors noted that three factors must be observed to achieve optimal benefit with NDMRs as pretreatments. First, the NDMR must be dosed based on body weight. Second, the time interval of 3 minutes between pretreatment and Sch should be adhered to. Last, the Sch dose should be 2 mg/kg.

After analysis of their data, the authors stated the ideal combination that prevented fasciculations, provided the best intubating conditions, and had the lowest incidence of postoperative myalgias was dTc 0.07 mg/kg 3 minutes prior to Sch 2 mg/kg. The second best combination was gallamine 0.2 mg/kg and Sch 2 mg/kg. Pancuronium 0.01 mg/kg and 0.02 mg/kg in combination with Sch 2 mg/kg were satisfactory, although much less efficient than the combinations with dTc or gallamine.

Brodsky, Brock-Utne, and Samuels (1979) also studied pancuronium as a pretreatment. Their study focused on the prevention of postoperative myalgias, but fasciculations and intubating conditions were also observed. Forty adult patients were randomly divided into two groups. Group I (n = 20) received pancuronium 1 mg 4 minutes prior to Sch 1.5 mg/kg. Group II (n = 20) received only Sch 1.5 mg/kg for muscle relaxation. Induction of anesthesia was standardized with thiopentone 4 mg/kg. Tracheal intubation was performed 60 seconds after the injection of Sch. The researchers were blinded until the completion of the study.

Both groups were similar in regards to demographic data. Relaxation was adequate for tracheal intubation in all patients. The incidence of fasciculations in Group I was 20%, but only one of these had vigorous fasciculations. In Group II, 95% of the patients experienced fasciculations, with 65% demonstrating vigorous fasciculations. The occurrence of postoperative myalgia was 20% for Group I and 35% for Group II. There was no correlation with fasciculations and the development of postoperative myalgias. The authors concluded the routine practice of pretreating with pancuronium 1 mg 4 minutes prior to Sch 1.5 mg/kg prevented muscle fasciculations but did not decrease the incidence or severity of postoperative myalgias.

Blitt et al. (1981) compared dTc, gallamine, metocurine, and pancuronium as pretreatment agents. Eighty adult ASA I or ASA II patients were randomly divided into 8 groups of 10 subjects each. Six of the 8 groups were given a selected dose of a NDMR as a pretreatment and 2 groups were not pretreated and served as controls. The pretreatment regimes consisted of gallamine 20 mg, dTc 3 mg, pancuronium 0.5 mg, and metocurine 1, 1.5, and 2 mg. All pretreatment groups received Sch 1.5 mg/kg 3 minutes after the NDMR. One control group received Sch 1.0 mg/kg and the other received Sch 1.5 mg/kg. Clinical relaxation and intubating conditions were assessed on a five point scale where 0 = poor relaxation/unable to intubate, 4 = optimum

relaxation/excellent intubating conditions, and 1, 2, and 3 were varying degrees of relaxation between 0 and 4. The presence and degree of fasciculations were evaluated on a 4 point scale where 0 = no fasciculations, 3 = vigorous fasciculations and 1 and 2 were varying degrees of fasciculations between 0 and 3.

All 8 groups were homogenous with regard to age, gender, and weight. There was no significant difference between groups concerning intubating conditions. All patients in the control groups exhibited fasciculations. The incidence of fasciculations was 30% for the pancuronium group and 10% for the 2 mg metocurine group. The only statistically significant difference the authors achieved regarding fasciculations compared the pretreated groups to the control groups ($p < .001$). The authors summarized that 1 mg metocurine, 20 mg gallamine, or 3 mg dTc could be used interchangeably as pretreatments 3 minutes prior to Sch 1.5 mg/kg. Pancuronium was again unsuitable as a pretreatment to prevent Sch-induced fasciculations.

By 1988 interest arose concerning the site of action of NDMRs at the neuromuscular junction. Evidence suggested that muscle pain was related to the rate of motor end plate unit firing, not to visible fasciculations. Also, it was postulated that NDMRs modified fasciculations and postoperative myalgias by preventing prejunctional depolarization and local axon reflexes, thereby decreasing

the rate of motor unit firing. O'Sullivan, Williams, and Calvey (1988) studied the effect of pretreatment with Sch, gallamine, or pancuronium on fasciculations and postoperative myalgias. Gallamine was chosen because previous research demonstrated a predominately prejunctional effect when compared to pancuronium.

Sixty adult female patients were randomly assigned to 1 of 4 groups. Group I (n = 15) received normal saline 45 seconds prior to Sch 1.5 mg/kg to serve as control. Group II (n = 15) received Sch 10 mg 45 seconds prior to Sch 1.5 mg/kg. Group III (n = 15) received gallamine 20 mg 45 seconds prior to Sch 1.5 mg/kg. Group IV received pancuronium 1 mg 45 seconds prior to Sch 1.5 mg/kg. Induction of anesthesia was standardized with thiopentone 4 mg/kg. The presence and degree of fasciculations were assessed on a 4 point rating scale similar to previous studies. Postoperative myalgias were assessed on a 4 point rating scale at 24, 48, and 72 hours.

The authors found no correlation between the fasciculation score and postoperative myalgias at 24, 48, and 72 hours. Some patients had high fasciculation scores and low myalgia scores, while others had low fasciculation scores and high myalgia scores. Pretreatment with Sch produced no significant effect on either the fasciculation score or the myalgia score. Gallamine significantly decreased the fasciculation score ($p < .05$) when compared to

the control group. Gallamine also decreased the postoperative myalgia scores but the differences were not statistically significant. Pancuronium decreased the fasciculation score but to a lesser extent than gallamine. Pancuronium significantly decreased ($p < .05$) the postoperative myalgia scores at 24 and 48 hours. The authors concluded their findings were consistent with previous studies regarding fasciculations and postoperative myalgias.

Vecuronium. Early in the 1980s vecuronium arrived in the clinical anesthesia arena as the newest NDMR. Studies soon followed that evaluated its potential for abolishing fasciculations and decreasing postoperative myalgias. Ferres et al. (1983) randomly divided 198 adult ASA I patients into 9 groups, with at least 20 patients in each group. Pretreatment regimes consisted of vecuronium 1 mg, gallamine 20 mg, pancuronium 1 mg, and dTc 3mg given either 1 or 2 minutes prior to Sch 1.5 mg/kg. A control group received normal saline 1 minute prior to Sch 1.5 mg/kg. Anesthesia was induced with thiopentone 5 mg/kg. Fasciculations were graded as absent, moderate, or severe. Postoperative myalgias were assessed at 24 and 48 hours.

All demographic data between the nine groups were similar with regards to age, weight, and gender. The lowest frequency of pain was found in the Vec 2 minute group ($n = 27$) which was 18.5%. The authors noted that the difference

in the overall occurrence of postoperative myalgia over the 48 hours was not different whether the pretreatment was administered 1 or 2 minutes prior to Sch. Although the pretreatment regimes significantly reduced the frequency and intensity of fasciculations ($p < .05$), the authors found no correlation between fasciculations and the occurrence of postoperative myalgias.

In 1990, Mingus, Herlich, and Eisenkraft studied the incidence of fasciculations and postoperative myalgias in 100 female outpatients who had laparoscopic surgery. Four groups of 20 patients each were pretreated with normal saline (Group I), dTc 0.05 mg/kg (Group II), vecuronium 0.006 mg/kg (Group III), or midazolam 0.025 mg/kg (Group IV) 3 minutes prior to Sch 1.5 mg/kg. Group V ($n = 20$) received Vec as the sole muscle relaxant. This was a prospective, double-blinded, randomized study. Fasciculations were rated on a 0 to 3 scale similar to previous studies (0 = no fasciculations, 1 = mild fasciculations, 2 = moderate fasciculations, 3 = severe, vigorous fasciculations). Postoperative myalgia was also scored on a 0 to 3 scale where 0 = no pain, 1 = mild, 2 = moderate, and 3 = severe.

There were no significant difference in mean age or weight between the 5 groups. Data were analyzed by analysis of variance, chi-square, and contingency coefficient analysis. A value of $p < .05$ was considered significant.

Fasciculations occurred most frequently in the control group (95%), with 70% being rated as moderate. Not surprisingly, no fasciculations occurred in Group V where vecuronium was the only muscle relaxant used. In Groups II and III fasciculations occurred 15 and 25%, respectively. After analysis, the authors found no difference in the incidence of fasciculations among Groups II, III, and V, or between Groups I and IV. The incidence of fasciculations was significantly greater in Groups I and IV than in Groups II, III, and V (p = .0001). No significant differences in the severity of fasciculations was found between Groups I and IV, or between Groups II, III, and V. The authors also identified no association between the severity of fasciculations and the development of postoperative myalgia between the pretreatment groups. The researchers concluded that vecuronium, but not midazolam, was as effective as dTc in decreasing the incidence of Sch-induced fasciculations.

Oshita et al. (1991) compared dTc, pancuronium, and vecuronium as pretreatment regimes. Thirty-two adults were randomly assigned to 1 of 5 groups. Group I (n = 7) received 3 ml normal saline. Group II (n = 7) received Sch 1 mg/kg. Group III (n = 6) received dTc 0.08 mg/kg. Group IV (n = 5) received pancuronium 0.01 mg/kg. Group V (n = 7) received vecuronium 0.01 mg/kg. Groups III, IV, and V received the pretreatment doses 5 minutes prior to Sch 1 mg/kg.

Statistical analyses were performed by analysis of variance and chi square analysis. Chi-square analysis was performed to compare proportions of patients assigned to graded categories representing intensity of fasciculations. A p value of $< .05$ was pre-established as significant. The intensity of fasciculations were evaluated visually and scored on a 0 to 3 scale similar to the one used by Mingus, Herlich, and Eisenkraft (1990).

The incidence of fasciculations in Group II was 100%, with 42% being scored as severe and 58% being moderate. Surprisingly, the incidence of fasciculations in Groups III, IV, and V was 0%. This was a significant finding ($p < .05$). The authors summarized that dTc, pancuronium, and vecuronium significantly and equally abolished Sch-induced fasciculations.

Atracurium. In the 1980s a second intermediate-acting NDMR was developed and released into clinical anesthesia practice. This new NDMR was atracurium. By 1985 research was conducted to test its potential for fasciculation attenuation and postoperative myalgia prevention.

One such study was conducted by Budd, Scott, Blogg, and Goat (1985). They studied 100 patients who were randomly assigned to 1 of 4 groups. Group I ($n = 25$) received atracurium 2.5 mg. Group II received atracurium 5 mg. Group III ($n = 25$) received fazadinium 3.75 mg. Group IV

(n = 25) received normal saline 3 ml. All pretreatments were administered 3 minutes prior to Sch 1 mg/kg. Fasciculations were noted as present or absent.

The incidence of fasciculations in Group IV was 96%. In Groups I and III fasciculations occurred in 32% of the patients, while in Group II fasciculations occurred only in 16% of patients. The authors noted that the incidence of fasciculations was significantly less ($p < .01$) in all pretreatment groups. The authors also identified no relationship between the occurrence of fasciculations and the development of postoperative myalgia.

Another study in 1985 was performed by Manchikanti et al. The purpose of the study was to evaluate atracurium as a prophylaxis against Sch-induced fasciculations and postoperative myalgia. Eighty patients were randomly allocated to 1 of 4 groups with 20 patients in each group. Pretreatments were administered in a double blinded fashion and consisted of either normal saline or atracurium.

Patients in Groups I and II served as controls and received normal saline for pretreatment, followed 3 minutes later by Sch 1.0 mg/kg (Group I) or 1.5 mg/kg (Group II). Patients in Groups III and IV received atracurium 0.05 mg/kg pretreatment, followed 3 minutes later by Sch 1.0 mg/kg (Group III) or 1.5 mg/kg (Group IV). The intensity of fasciculations was evaluated visually and scored on a 0 to 3 rating scale. The scale was the same as the one used by

Manchikanti (1984). Postoperative myalgia was evaluated at 24 and 48 hours postoperatively.

Statistical analyses were performed by analysis of variance chi square analysis. Overall and follow-up chi square analysis were performed to compare proportions of patients in the 4 groups assigned to graded categories representing intensity of fasciculations. Results were considered statistically significant if p values were $< .05$.

Demographic data did not differ significantly between the 4 groups. There were significant differences between the 4 groups with respect to mean fasciculation intensity ($p = .0003$). Groups III and IV had significantly lower mean fasciculation intensity than Group I and II ($p < .05$). There were no significant differences between either Groups I and II or Groups III and IV. The 4 groups also differed significantly in terms of proportion of patients with fasciculations ($p = .003$). Groups III and IV had significantly fewer patients with fasciculations than the 2 control groups ($p < .05$). The authors concluded that atracurium was effective in attenuating Sch-induced fasciculations.

In 1987, Sosis, Broad, Larijani, and Marr compared atracurium to dTc for prevention of Sch-induced fasciculations. Forty-four ASA class I or II women undergoing laparoscopic surgery were randomly assigned to 1 of 3 groups. Group I ($n = 13$) received atracurium

0.025 mg/kg. Group II (n = 17) received dTc 0.05 mg/kg. Group III (n = 14) received normal saline and served a controls. All pretreatments were administered in double-blinded manner and were followed 3 minutes later by Sch 1.5 mg/kg.

The presence and intensity of fasciculations were visually assessed and scored on a 0 to 3 rating scale. This scale had previously been used by Manchikanti (1984, 1985). Multivariate analysis of variance, followed by Duncan's multiple range test and Fisher's exact probability test were performed to detect any statistically significant differences in dependent variables among the groups. A p value of $< .05$ was pre-established as significant.

There were no significant differences between the groups in terms of age and weight. Violent fasciculations were not observed in any patient. After atracurium, 31% of the patients had mild and 15% had moderate fasciculations. Fasciculations were mild in 6% and moderate in 6% of patients in the dTc group. In the control group, fasciculations were mild in 36% and moderate in 43% of the patients. The authors found no correlation between fasciculations and the development of postoperative myalgia. They summarized by stating that although atracurium was significantly better than normal saline for attenuating fasciculations, dTc was superior.

Erkola (1990) compared atracurium, Vec, dTc, and alcuronium as pretreatments for preventing Sch-induced fasciculations and postoperative myalgias. Two-hundred fifty women undergoing termination of pregnancy during the first trimester were randomly assigned to 1 of 5 groups. Each group consisted of 50 patients. Either alcuronium (0.03mg/kg), atracurium (0.04 mg/kg), dTc (0.05 mg/kg), or Vec (0.01 mg/kg) was administered 4 minutes prior to Sch 1.5 mg/kg. An additional 50 patients were given normal saline 4 minutes prior to Sch 1.0 mg/kg to serve as controls.

After the Sch, the sites of fasciculations were recorded and their intensity was graded as follows: 0 = absent, 1 = fine tremor, 2 = moderate fasciculations, and 3 = strong contractions. Statistical analysis was performed using the SPSS/PC+ statistical program. The one-way analysis of variance (ANOVA) was used for parametric data. Kruskal-Wallis one-way ANOVA and the chi-square test were used for non-parametric data. The Mann-Whitney U-test was used for group comparisons in Sch-induced fasciculations and postoperative myalgia. Regression lines for correlation between fasciculations and postoperative myalgia were calculated after the least squares method. A pre-established level of $p < .05$ was considered as statistical significance.

There were no demographical differences between the groups with regard to age and weight. All pretreatment regimes prevented Sch-induced fasciculations better ($p < .001$) than normal saline. Alcuronium and dTc were more effective ($p < .01$) than atracurium or Vec. Alcuronium and dTc prevented fasciculations in 90% of patients while atracurium and Vec prevented them in 68% of patients. Compared to the other groups, the saline group experienced significantly more ($p < .001$) fasciculations and myalgia.

Mivacurium

Mivacurium is the newest NDMR to enter the clinical anesthesia arena. It is classified as a short-acting NDMR with a duration of action between Sch and Vec. A review of the literature found that Miv has not been studied as a pretreatment to prevent Sch-induced fasciculations.

Three Minute Time Interval

The optimal time interval between the administration of the NDMR pretreatment and the intubating dose of Sch has been a source of disagreement. Ferres et al., (1983) compared Vec, pancuronium, gallamine, and dTc as pretreatments with 1 and 2 minute time intervals before Sch administration. Their results demonstrated that gallamine was the only NDMR effective in preventing fasciculations. Gallamine prevented fasciculations in 80% of patients at 1

minute and 75% at 2 minutes. Fasciculations occurred from 40 to 67% of the time when the other NDMRs were administered.

In another study, O'Sullivan, Williams, and Calvey (1988) compared gallamine to pancuronium as pretreatments 1 minute before Sch. Their results were similar to Ferres et al. in that gallamine was effective in preventing fasciculations but pancuronium was not. The authors suggested using a longer time interval if the pretreatment was not gallamine.

Other studies have investigated longer time intervals. Manchikanti (1984) used a 4 to 5 minute interval when he compared dTc to diazepam as a pretreatment. The results of this study demonstrated that dTc was highly effective ($p = .0001$) in preventing fasciculations when administered 4 to 5 minutes prior to Sch. The author recommended a time interval of at least 4 minutes when using dTc as a defasciculator.

Erkola (1990) also used a 4 minute latency period when he compared alcuronium, atracurium, dTc, and Vec as pretreatments. The results of this study were comparable to Manchikanti's (1984) findings. Alcuronium and dTc prevented fasciculations in 90% of patients while fasciculations were prevented in 68% of patients pretreated with Vec or atracurium. The author concluded that the 4 minute time interval as adequate when using NDMRs as pretreatments.

The most favorable time interval in previous studies has been 3 minutes. Bennike and Nielsen (1964) investigated time intervals of 2, 3, and 8 minutes using dTc as the pretreatment. The authors found the optimal interval for preventing fasciculations was 3 minutes. The worst interval was 8 minutes followed by 2 minutes.

This time interval of 3 minutes was also confirmed to be the best when using NDMRs as pretreatments by Takki, Kauste, and Kjeliberg (1972), and Harrow and Lambart (1984). Since the mid-1980s, most researchers have used the 3 minute latency period for preventing Sch-induced fasciculations (Blanc, Vaillancourt, Brisson 1986; Budd, Scott, Blogg & Goat, 1985; Manchikanti, et al., 1985; Marr & Sosis 1989; Mingus, Herlich, & Eisenkraft 1990; Sosis, et. al. 1987).

Pretreatment Doses Based on IBW

Since the classic study of Churchill-Davidson (1954) demonstrated that 40 mg of gallamine prevented Sch-induced fasciculations, a multitude of NDMRs and various dosage regimes of NDMRs have been manipulated. Some researchers used fixed dose regimes of NDMRs as pretreatments (Blitt et al., 1981; Budd, Scott, Blogg, & Goat, 1985; Ferres et al., 1983; Masey, Glazebrook, & Goat, 1983; O'Sullivan, Williams, & Calvey, 1988). Others have advocated doses of NDMRs based on body weight (Blanc, Vaillancourt, & Brisson, 1986; Erkola, 1988; Erkola, 1990; Manchikanti et al., 1985; Marr &

Sosis, 1989; Mingus, Herlich, & Eisenkraft, 1990; Oshita et al., 1991; Sosis et al., 1987).

A review of the literature fails to identify a study that has used NDMRs as pretreatments based on IBW. Also, no study was performed using IBW to calculate the intubating doses of Sch. Cheymol (1988) suggested that hydrophilic medication dosages should be based on IBW.

Succinylcholine Doses

The normal IV dose of Sch given to facilitate tracheal intubation is 1 mg/kg. This is the case when Sch is the sole muscle relaxant used. However, when NDMRs are administered as pretreatments, the recommended Sch dose is increased to 1.5 mg/kg. The rationale for the increased Sch dose is that NDMRs are competitive antagonists of a Sch-induced block. Therefore, for Sch to overcome this competitive antagonism the initial IV dose is increased by 50% (Bevan & Donati, 1985; Choi, Gergis & Sokol, 1984; Lebowitz & Ramsey, 1989; Miller, 1989; Miller & Savarese, 1990; Stoelting, 1991).

Summary

This review of the literature demonstrated differing results on the efficacy of using NDMRs as pretreatments in preventing Sch-induced fasciculations. The studies indicated the presence and intensity of fasciculations were

reduced with NDMRs with pretreatment prior to Sch. No previous study has used IBW to calculate muscle relaxant dosages. Equipotent pretreatment doses of Miv and Vec were compared. The present study was undertaken to determine if Miv could attenuate Sch-induced fasciculations as effectively as Vec.

Chapter Three

Methodology

Research Design

To answer the question, is mivacurium as effective as vecuronium in suppressing succinylcholine-induced fasciculations, a quasi-experimental design was chosen. All doses of Sch, Miv, and Vec were calculated based upon IBW. There were 2 experimental groups and 1 control group. The independent variables Vec 0.01 mg/kg (IBW) and Miv 0.02 mg/kg (IBW), were manipulated while the dependent variable, Sch-induced fasciculations, was observed. The latency period of 3 minutes and the dose of Sch (IBW) were treated as fixed variables. The control group received a saline placebo. Patients were randomized by use of a computer generated table of random numbers.

Selection of group assignments was double blinded in the following way. A non-participating colleague created a roster of patient numbers (1-60) and assigned groups (I, II, or III) based on the table of random numbers. A master list of patient numbers and group assignments was made and placed in a sealed envelope for future data analysis. Another copy

of the roster with patient numbers and group assignments was cut into individual strips, folded and placed into a bag. This method blinded the investigator to the group assignments.

The investigator calculated all dosages as if the subject would receive all three regimes and presented the research instrument to the primary anesthesia provider. At that point, the provider selected on folded slip of paper from the bag that had both a patient number and treatment group number. The patient number was written on the research instrument (see Appendix A). Medications were prepared by the primary anesthesia provider as dictated by the selected treatment group and the slip of paper was destroyed.

After waiver of consent was obtained from the Committee on the Conduct of Human Research, subjects were selected from the daily operating room schedule who met the inclusion criteria. Each subject was taken to the surgical suite and placed on the surgical table. Routine monitors were attached and preoxygenation begun. The primary anesthesia provider gave his/her choice of medication to blunt laryngoscopy. He/she then informed the investigator of the injection of the defasciculating dose (time = 0 minutes) and timing began using a wall clock located in all surgical suites. At 2 minutes from the injection of the defasciculating dose, the anesthesia provider administered

an induction dose of the anesthetic of his/her choice. Upon the loss of lid reflex manual ventilation was attempted; when successful, isoflurane was started at the anesthesia provider's discretion. At 3 minutes, the investigator instructed the anesthesia provider to administer the Sch.

The subject was then observed for fasciculations and intubated when judged to be clinically appropriate. Two investigators recorded the incidence and intensity of fasciculations on a 0 to 3 rating scale. A score of 3 indicated vigorous muscle contractions of the face, upper torso, and/or upper extremities. A score of 2 indicated moderate muscular contractions of the face, upper torso, and/or upper extremities. A score of 1 indicated very fine muscular contractions of the face, upper torso, and/or upper extremities. A score of 0 indicated no visible fasciculations. After the subject was intubated, the primary anesthetist provided anesthesia at his/her discretion.

Population, Sample, and Setting

A nonprobability sample of convenience was obtained from a population of patients undergoing elective surgery requiring general endotracheal anesthesia at a 1052 bed mid-Atlantic university teaching hospital. Sixty patients were chosen who met the following criteria: Adult, 18-75 years old, ASA I or II without significant neuromuscular, hepatic,

renal, or cardiovascular disease. Parturients, children, ASA III and IV patients were excluded from this study.

Treatment Groups

Group I was the control group. Two milliliters of 0.9% normal saline was given 3 minutes prior to Sch 1 mg/kg (IBW). Group II was given Vec 0.01 mg/kg (IBW) 3 minutes prior to Sch 1.5 mg/kg (IBW). Group III was given Miv 0.02 mg/kg (IBW) 3 minutes prior to Sch 1.5 mg/kg (IBW).

Analysis of Data

The continuous variables of age, height, and weight were analyzed by one-way Analysis of Variance. Counts of the discrete variables, gender, and fasciculations, were analyzed by Chi-square tests. Overall and follow-up Chi-square analyses were performed to compare proportions of subjects in the 3 groups assigned to graded categories representing intensity of fasciculations. Results were considered statistically significant if p values were $< .05$.

Chapter Four

Results

Analysis of Data

Sixty ASA class I and II general surgical patients were randomly assigned to 1 of 3 groups. Group I (n = 20) received normal saline as a pretreatment and served as controls. Group II (n = 20) patients received Vec 0.01 mg/kg as a pretreatment. Group III (n = 20) patients received Miv 0.02 mg/kg as a pretreatment. The dichotomous variables gender, fasciculations, and intensity of fasciculations, were analyzed by the Chi-square test of independence. The continuous variables, age, height, and weight were analyzed by one-way analysis of variance. There were no significant differences between the groups with regard to age, height, weight, and gender.

Age

The age of the patients ranged from 18 to 75 years. Group II had the lowest mean age (42.65 years). Group I had the highest mean age (48.8 years). These differences were

not significant (p = .39). Thus, the groups did not differ with respect to age (see Table 1).

Height

No significant differences were found between the groups with respect to height (p = .4009). The mean height was highest in Group III (170.69 cm) and lowest in Group II (161.93 cm) (see Table 1).

Weight

The smallest mean weight was in Group III (81.95 kg) and the largest in Group II (86.65 kg). No significant differences were found between the groups with respect to weight (p = .6576) (see Table 1).

Gender

More females (33) than males (27) participated in this study. Group III had the largest number of females (12) and Group I the smallest (10). These differences were not significant (p = .82) (see Table 1).

Table 1

Demographic Variables

	Age[1] (yr) M +/- SD	Weight[2] (Kg) M +/- SD	Height[3] (cm) M +/- SD	Gender M/F
Group I	48.8 ± 12.4	85.4 ± 13.1	170.56 ± 9.9	10/10
Group II	42.7 ± 13.2	86.7 ± 19.9	161.93 ± 9.9	9/11
Group III	45.6 ± 16.0	82.0 ± 16.6	170.69 ±	8/12

Note. 1 = (p = .3896), 2 = (p = .4009), 3 = (p = .6576), 4 = (p = .82). No significant difference(p > .05). M = males, F = females, m = mean, SD = standard deviation.

Fasciculations

Chi-square analysis of the observable variable, fasciculations, demonstrated significant differences between the control group and the experimental groups (p = .0001). However, no significant differences were found between the Miv and Vec groups (p = .2059). The incidence of fasciculations was highest in the control group (90%) and lowest in the Vec group (40%) (see Table 2).

Table 2

Incidence of Fasciculations

Group I (20) (saline)	Group II (20) (Vec)	Group III (20) (Miv)
90% (18)*	40% (8)**	60% (12)**

Note. * = significantly different from ** (p = .0001). ** = not significantly different from each other (p > .2059).

Intensity of fasciculations

The intensity of fasciculations were graded on a 4 point scale (0 = no observable fasciculations, 1 = mild, 2 = moderate, and 3 = severe fasciculations). Chi-square analysis revealed no significant differences between the Vec and Miv groups (p > .9999). Significant differences were found between the control group and treatment groups (p < .0001) (see Table 3). Intensity of fasciculations was lowest in the Miv group with all 20 patients experiencing mild or no fasciculations. The control group had the most intense fasciculations with 70% being graded as moderate or severe (see Table 4).

Table 3

Fasciculation Intensity

Fasciculation Score	Group I * (saline) (%)	Group II ** (Vec) (%)	Group III *** (Miv) (%)
0	2 (10)	12 (60)	8 (40)
1	4 (20)	7 (35)	12 (60)
2	11 (55)	0 (0)	0 (0)
3	3 (15)	1 (5)	0 (0)

Note. ** = Significantly different from *, but not significantly different from each other.

Table 4

Intensity of Fasciculation Score Combined

Fasciculation Score	Group I (saline) (20)	Group II (Vec) (20)	Group III (Miv) (20)
0 - 1	30% (6)	95% (19)	100% (20)
2 - 3	70% (14)	5% (1)	0% (0)

Note. 0 - 1 = absent or mild and 2 - 3 = moderate or severe.

Chapter Five

Discussion

Introduction

This study sought to determine if Miv is as effective as Vec in attenuating Sch-induced fasciculations. The hypothesis tested was as follows: there is no significant difference in the incidence of fasciculations in the face, upper torso, and upper extremities of ASA I and ASA II patients who received a defasciculating dose of saline (control), Vec or Miv (based on IBW) prior to an intubating dose of Sch (also based on IBW). Chi-square analysis revealed significant differences ($p = .0001$) between the control group and the experimental groups, with regards to the incidence and intensity of fasciculations. However, no significant differences were obtained between the Vec and Miv groups with respect to both the incidence and intensity of fasciculations ($p = .2059$ and $p > .9999$, respectively). Therefore the hypothesis is rejected. The statistical analysis of the demographic data determined that the groups did not differ with regard to age, height, weight, and gender.

Correlation of Findings With Previous Studies

Incidence of fasciculations. Chi-square analysis of the incidence of fasciculations revealed significant differences between the control group (saline) and the experimental groups. This study demonstrated that both pretreatments (Vec and Miv) were significantly better than saline in attenuating Sch-induced fasciculations (p = .0001). Significant differences between the Miv and Vec groups were not found.

The protocol of the present study closely followed the protocols of Erkola (1990), Mingus, Herlich, and Eisenkraft (1990), and Sosis et al. (1987), with minor deviations. Erkolas' (1990) study population was female and the latency period was 4 minutes. The populations of Mingus, Herlich, and Eisenkraft (1990) and Sosis et al, (1987) were also female and all groups received Sch 1.5 mg/kg, the saline (control) group included. Even with these deviations, the results obtained in this study support the findings of the above mentioned studies. That is, all pretreatment regimes attenuated Sch-induced fasciculations significantly better than saline. Also, consistent with the findings of this study, the previous studies failed to find a significant difference between the NDMRs used as pretreatments.

Intensity of fasciculations. Chi-square analysis demonstrated differences in the intensity of fasciculations

between the control group and both the experimental groups ($p < .0001$). No significant differences were obtained between the Vec and Miv groups ($p > .9999$). The structured observation technique used in this study to grade the intensity of fasciculations was used by previous researchers (Blitt et al., 1981; Erkola, 1990; Manchikanti, 1984; Manchikanti et al., 1985; Sosis et al., 1987). In the present study, the control (saline) group experienced significantly ($p < .0001$) more intense fasciculations than the experimental groups. Although the intensity of fasciculations was reduced in both experimental groups, no statistically significant differences ($p > .9999$) between them were found. These results are congruent with the findings of previous studies (Blitt et al., 1981; Erkola, 1990; Manchikanti, 1984; Manchikanti et al., 1985; Sosis et al., 1987).

Limitations

The major limitation of this study was time. Data collection was limited to a 6 week period when the researcher was assigned to a clinical rotation at a mid-Atlantic university-based teaching hospital. Because of time constraints, the sample size was relatively small ($N = 60$), with only 20 patients per treatment group. Also, because Miv has not previously been studied as a pretreatment to attenuate Sch-induced fasciculations,

general assumptions should not be drawn due to the small Miv experimental group (n = 20). A larger sample size may have been beneficial.

Another limitation was the fasciculation intensity scale. The presence and degree of fasciculations were graded on a 0 to 3 scale by a structured observation technique. This technique has previously been used by several researchers, and while appearing to be a reliable and valid technique, it limits measurements to the observation skills of the recorder.

Recommendations for Future Study

In order to expand the findings of this study, several suggestions are made for future research. The first involves the level of measurement used for data collection. An instrument, such as a myograph, could be employed which would allow for a better delineation of fasciculation intensity. This, in turn, would permit more stringent statistical testing.

A second recommendation for future study involves time. An adequate amount of time for data collection would allow the researcher to control any preoperative medications, have a larger sample size, and standardize the induction technique.

A third suggestion would be to duplicate the present study and observe for side effects which may occur with

pretreatments. Patient anxiety, partial paralysis, and apnea have been associated with pretreatment doses of NDMRs. It would be interesting to determine if these side effects would be attenuated by using muscle relaxant doses based on IBW.

Finally, the finding of the present study have supported that pretreatment with Miv is an effective mode of attenuating Sch-induced fasciculations. It would be interesting to duplicate previous studies, using Miv, to determine if it is effective in preventing myalgias and increases in intraocular and intragastric pressures. Research of this type might help to resolve some of the discrepancies found from the review of previous studies.

Clinical Significance

Formulating a cost-effective anesthetic plan is becoming ever important with the price of health care drastically increasing. The results of this study demonstrated that Miv was as effective as Vec in attenuating Sch-induced fasciculations. The cost of Miv is $8.04 for a 5 ml vial (10 mg) and $12.56 for a 10 ml vial (20 mg). Vecuronium costs $16.83 for a 10 mg vial and must be reconstituted with a sterile diluent (saline or water) which adds further cost to the patient. Thus when comparing equivalent pretreatment cost, Miv is the superior agent.

Summary

The purpose of this study was to determine if Miv was as effective as Vec in attenuating Sch-induced fasciculations. Although fasciculations are not life threatening, they have been associated with myalgias and increases in intracranial, intragastric and intraocular pressures. Therefore, anesthesia providers attempt to attenuate the fasciculations by giving small subparalytic doses of NDMRs. Vec and Mivacurium have therapeutic value in achieving this goal.

The results of this study demonstrated that Miv was as effective as Vec in attenuating Sch-induced fasciculations. There were no significant differences between Vec and Miv; however, there were significant differences when comparing saline to Vec or Miv. Vecuronium or Mivacurium (given in doses based on IBW) 3 minutes prior to an intubating dose of Sch (also based on IBW) decreased the incidence and intensity of Sch-induced fasciculations. Also, Miv is more cost effective than Vec in attenuating Sch-induced fasciculations.

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Appendix

APPENDIX A

Research Instrument

Patient Initials_____Patient Hospital Number_____
Patient Assigned Study #_____Treatment Group #_____
Age_____Surgical Procedure_____
Sex_____Weight (lbs)_____Weight (kgs)_____
Height (in)_____Ideal Body Weight (Ht. x 2.5 - 100)_____
Induction Agents_____mg
_____mg
_____mg
_____mg

Treatment Groups

Grp I. Saline 2 ml
Succinylcholine 1 mg/kg(IBW)___mg+___ml saline =9ml
Grp II. Vecuronium 0.01 mg/kg(IBW)___mg+___ml saline =2ml
Succinylcholine 1.5 mg/kg(IBW)___mg+___ml saline =2ml
Grp III. Mivacurium 0.01 mg/kg(IBW)___mg+___ml saline = 2ml
Succinylcholine 1.5 mg/kg (IBW)___mg+___ml saline =9ml

Protocol

1. Obtain permission of primary anaesthesia provider.
2. Review patient chart for study inclusion criteria.
3. Calculate and prepare study treatment drugs.
4. Primary anesthesia provider selects study # and group # from bag.
5. Discard syringes not to be used.
6. Connect routine monitors and begin preoxygenation.
7. Record baseline vital signs.
8. Begin giving drug(s) of choice to blunt laryngoscopy.
9. Time 0 minutes, give pretreatment.
10. Time 2 minutes, give induction agent and ventilate at loss of lid reflex; turn on Forane.
11. Time 3 minutes, give intubating dose of Sch.
12. Observe and record fasciculations on the 0 to 3 rating scale.
13. Intubate when clinically appropriate.
14. Continue anesthetic regime as dictated by patient needs.

Fasciculations

None (0)_____ No observable fasciculations
Fine (1)_____ Fine muscular contractions of the face, upper torso and/or upper extremities
Moderate (2)___ Moderate muscular contractions of the face, upper torso and/or upper extremities
Severe (3)_____ Severe muscular contractions of the face, upper torso and/or upper extremities

Vita