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MONITORING NEUROMUSCULAR BLOCKADE AT THE ADDUCTOR POLLICIS AND ORBICULARIS OCULI WITH SPLIT DOSING OF MIVACURIUM CHLORIDE

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MONITORING NEUROMUSCULAR BLOCKADE AT THE ADDUCTOR POLLICIS AND ORBICULARIS OCULI WITH SPLIT DOSING OF MIVACURIUM CHLORIDE

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

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Table of Contents

List of Figures

Abstract

MONITORING NEUROMUSCULAR BLOCKADE AT THE ADDUCTOR POLLICIS AND ORBICULARIS OCULI WITH SPLIT DOSING OF MIVACURIUM CHLORIDE.

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Twenty ASA class I and II patients between the ages of 15 and 64 years undergoing surgical procedures requiring neuromuscular blockade and general anesthesia were selected at random to participate in this study. Patients taking medication known to interfere with neuromuscular blockade were excluded. All patients were given 2 mg of midazolam IV as a premedication. In the operating room, routine monitors were connected and baseline blood pressure, pulse and respirations were recorded with subsequent recordings at 5 and 10 minutes following induction of anesthesia.

Indirect stimulation of the ulnar nerve was achieved by placing ECG electrodes 2 cm and 10 cm proximal to the distal end of the ulnar nerve. The same type ECG electrodes were used at the orbicularis oculi muscle group. One electrode

was placed 2 cm lateral and 2 cm caudal to the outer canthus of the eye and the second 2 cm caudal to the first.

Induction of anesthesia was achieved with mivacurium 0.1 mg/kg IV followed by fentanyl 100 mcg IV and propofol 2 mg/kg IV. The second dose of mivacurium 0.1 mg/kg was administered 30 seconds after the initial dose. Baseline twitch response was started at both monitoring sites using 1 Hz twitch mode with an output of 60 mA. Each patient was monitored until there was a loss of twitch response at either of the two sites. When the twitch response was suppressed at one site, the anesthetist performed direct visual laryngoscopy. If the vocal cords were open, the trachea was intubated. The time of twitch suppression at the second site was also recorded. The data collected from the study was examined using a paired t-test and a comparison of the mean times to loss of twitch at the orbicularis oculi and the adductor pollicis was made. All 20 of the subjects lost the orbicularis oculi motor response to stimulation prior to the loss of motor response to stimulation at the adductor pollicis. The mean time to loss of twitch response was 85 seconds at the orbicularis oculi and 230 seconds at the adductor pollicis.

It was concluded that there is a shorter time to loss of twitch response at the orbicularis oculi than at the adductor pollicis using 0.2 mg/kg mivacurium chloride in equally divided doses given 30 seconds apart.

Chapter One

Introduction

Neuromuscular transmission blocking agents (NTBA) are common in today's anesthetic practice. Neuromuscular blockade provides skeletal muscle paralysis or relaxation. This paralysis or relaxation provides several advantages to the anesthetist and surgeon. During abdominal surgery, paralysis prevents coughing and movement during the closure of the abdominal fascia, thereby reducing the risk of bowel extrusion and accidental perforation. Relaxation of the chest wall musculature allows for easier ventilation and avoids the need for high ventilatory pressures, thus reducing the risk of barotrauma and injury to the bronchopulmonary tree. The use of NTBAs intra-operatively prevents patient movement, thus allowing delicate surgeries to be performed. Neuromuscular paralysis also provides superior exposure of the vocal cords during laryngoscopy and relaxes the upper airway musculature thereby preventing laryngospasm during instrumentation of the airway. Although neuromuscular blockade facilitates endotracheal intubation, it also increases the risk of aspiration of gastric

contents. Therefore, the time from onset of neuromuscular blockade to placement of the endotracheal tube is critical. Neuromuscular blockade is essential to insure successful outcomes for many types of surgical procedures, thus NTBA use is widespread in anesthesia.

Neuromuscular transmission blocking agents interfere with normal conduction of nerve impulses at the neuromuscular junction. This action leaves the skeletal musculature temporarily paralyzed. The onset and length of the paralysis is dependent on distribution and elimination of the NTBA administered. Since the first clinical use of d-tubocurare in 1942 by Griffith and Johnson (Calverley, 1992), many NTBAs have been introduced. Newer NTBAs have been developed to minimize the time to onset and time to recovery of neuromuscular blockade. The need for monitoring these newer, shorter acting NTBAs is essential for many of today's short outpatient procedures. Of equal importance is the need to monitor the degree of neuromuscular blockade to determine the optimal time for endotracheal intubation. Traditionally, numerous clinical signs have been monitored to assess the onset and recovery of neuromuscular blockade. At best, clinical signs are a crude measure of the onset and elimination of neuromuscular blockade. New monitoring modalities for more consistent and quantitative measurement of neuromuscular blockade need to be investigated.

In 1958, Christie and Churchill-Davidson described external nerve stimulation via a peripheral nerve stimulator (PNS), to assess the amount of neuromuscular blockade during the course of an anesthetic (Viby-Mogensen, 1990). The PNS gave practitioners a new and vital tool to quantitatively assess the onset and elimination of neuromuscular blockade. Peripheral nerve stimulators are used routinely today for assessing the optimal timing for endotracheal intubation and extubation.

Three methods of peripheral nerve stimulation used routinely today are single twitch, train-of-four and tetanus. The site most commonly monitored for peripheral nerve stimulation is the ulnar nerve which elicits a response of the adductor pollicis muscle. This stimulation causes the adduction of the thumb towards the midline of the palm. The adductor pollicis twitches are easily visualized and quantified using the PNS. The facial nerve may also be monitored via the orbicularis oculi muscle group. Stimulation of this muscle group elicits a winking motion of the eye and is also easily visualized and quantified. Both of these sites allow the anesthetist to monitor the onset and decline of neuromuscular blockade for endotracheal intubation and extubation.

Since the need to quantify neuromuscular blockade is clinically important, a comparison of different monitoring sites would be helpful. There are only a small number of

studies comparing the adductor pollicis and orbicularis oculi sites. For this reason, a simultaneous comparison of the loss of twitch response at the facial nerve and the ulnar nerve is made for this study. Mivacurium chloride, a new short acting nondepolarizing NTBA, is employed.

Statement of the Problem

Neuromuscular blockade of the laryngeal musculature allows for easier visualization and intubation of the trachea, but also increases the risk of accidental aspiration of gastric secretions. Therefore, the onset of neuromuscular blockade and the placement of the endotracheal tube need to be synchronous. This study is designed to compare the onset time for paralysis at the adductor pollicis and the orbicularis oculi muscle groups. Both groups are simultaneously monitored to see if one is a better predictor of the onset of vocal cord paralysis.

Hypothesis

There is no difference between the adductor pollicis and orbicularis oculi muscles in time to the loss of twitch response and intubating conditions of the vocal cords using 0.2 mg/kg mivacurium chloride in two equal divided doses, 30 seconds apart.

Variables

Independent. The independent variables are: 1) mivacurium chloride and 2) time to loss of twitch.

Dependent. The dependent variables are: 1) loss of the twitch response of the adductor pollicis muscle, 2) loss of the twitch response of the orbicularis oculi muscle and 3) intubating conditions of the vocal cords.

Definition of Terms

Adductor pollicis. The adductor pollicis is a flat triangular muscle responsible for the movement of the metacarpal of the thumb inward towards the palm.

Intubating conditions. Intubating conditions pertain to the quality of visualization and position of the vocal cords during direct visual laryngoscopy.

Mivacurium chloride. Mivacurium chloride is a short-acting nondepolarizing neuromuscular transmission blocking agent of the bis-benzylisoquinolinium diester class.

Orbicularis oculi. The orbicularis oculi is the muscular body of the eyelid composed of the palpebral, lacrimal and orbital muscles. Stimulation of the orbicularis oculi causes closure of the eyelid in a winking motion.

Twitch response. Twitch response is a single muscular contraction due to the electrical stimulation of a nerve.

Vocal cords. The vocal cords are two bands of elastic tissue stretching across the opening of the larynx with attachments to the thyroid cartilage and arytenoid vocal process.

Assumptions

1. Nerve stimulators used to simultaneously observe the twitch responses delivered the same current to the sites being monitored.

2. Placement of the leads for monitoring the orbicularis oculi and adductor pollicis were uniform for each patient.

3. Twitches elicited from the orbiculis oculi were not the result of direct muscle stimulation.

Limitations

1. Electrodes used for the PNS may not have delivered the full current to the monitoring site due to poor skin contact or an inadequate amount of conductive gel.

2. Deviations from normal anatomy may have caused sub-optimal placement of the monitoring electrodes thus eliciting a poor muscular response.

3. The PNS may not have delivered the set current due to malfunction of the device.

Delimitations

1. Patients selected for the study were ASA classification I or II, between the ages of 18 and 65 and between the weights of 45 to 100 kilograms(kgs).

2. The study was conducted at one large tertiary care medical facility.

3. Two identical nerve stimulators were used and checked for matching output delivery by the biomedical engineering department of the facility.

Conceptual Framework

Anatomy of the neuromuscular junction. The neuromuscular junction is one of the most researched and characterized vertebrate synapses. In man, motor efferent axons exit the anterior horns of the grey matter of the spinal cord and travel uninterrupted to the striated muscles of the body. Once outside the spinal cord they are known as the lower motoneurons (Bowman, 1980). As these motor efferent axons move further away from the spinal cord, extensive branching occurs at the nodes of Ranvier. A single axon, through its extensive branching, innervates many muscle fibers. The motoneuron and the muscle fibers it innervates is termed a motor unit. The number of muscle fibers innervated by an axon is dependent on the muscle fiber type. There are two types of muscle fibers in the

body, Type I (slow twitch) muscle fibers and Type II (fast twitch) muscle fibers. Muscles are made up of both Type I and Type II fibers, however the distribution of each type is different (Murphy, 1988). Larger muscle groups of the body such as the adductor pollicis are primarily Type I muscle fibers. Large muscles are generally involved in slow movement or posture and are considered fatigue resistant. Small muscles of the body responsible for rapid or fine movement are primarily made of Type II muscle fibers. The orbicularis oculi and the adductor muscles of the larynx are examples of Type II muscle groups. (Claassen & Werner, 1992; Johnson, Polgar, Weightman & Appleton, 1973). A single motoneuron axon's branches may innervate 5 to 15 Type II muscle fibers or 1,000 Type I muscle fibers (Bowman, 1980). As the motoneuron branches reach the muscle fiber, the axon loses its myelin sheath and further branching occurs. These fine terminal branches are called telodendria. These telodendria end with axon terminals that rest in the synaptic troughs on the surfaces of muscle fibers. The plasma membrane that surrounds the muscle fiber (sarcolemma) has many invaginations called synaptic folds or clefts (Kutchai, 1988). The junctional gap between the telodendria and the sarcolemma is about 60 nanometers wide. The space between the telodendria and the sarcolemma is filled with a rich mucopolysaccharide material similar to collagen and is called the basement membrane. This membrane serves as a

filter allowing the rapid passage of acetylcholine and as a structural support. This basement membrane also contains much of the acetylcholinesterase of the junction (Bowman, 1980). It is the area containing the telodendria axon terminal, the synaptic trough and the plasma membrane of the muscle fiber that is referred to as the neuromuscular junction (see Figure 1).

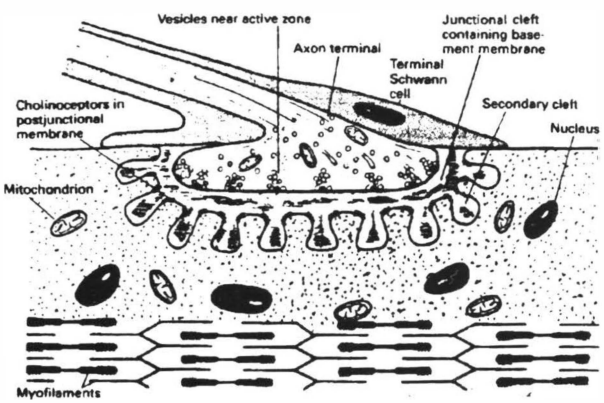

Figure 1. Diagram of neuromuscular junction.

Note. From Pharmacology of Neuromuscular function (p. 24) by W. C. Bowman, 1980, Baltimore: University Park Press.

Physiology of neuromuscular transmission. An action potential generated from a sensory receptor or by a voluntary decision made at higher brain centers travels down the terminal axon. Action potentials are self-propagating

waves of reversed membrane potential passing along a nerve or muscle fiber (Bowman, 1980). Action potentials eventually reach the lower motoneurons and telodendria causing depolarization of the pre-junctional membrane. This depolarization causes the release of the neurotransmitter acetylcholine into the synaptic cleft, which in turn causes the depolarization of the post-junctional membrane on the muscle cell by means of a receptor-agonist interaction. These events are near instantaneous, yet many events take place.

Acetylcholine synthesis. Synthesis of acetylcholine occurs in the motoneuron and its axons. Few other cells in the body are capable of this synthesis. The catalytic enzyme of the motoneuron, choline-O-acetyltransferase, causes the condensation of choline and acetyl coenzyme A to form acetylcholine (Kutchai, 1988). Most of the cells of the body manufacture acetyl coenzyme A from the breakdown of glucose (Lehninger, 1982). Choline is abundant in plasma and is actively transported into the motoneuron against a strong electrochemical gradient. The majority of the choline pumped back into the cell comes from the degradation of acetylcholine released from the pre-junctional membrane (Kutchai, 1988). The acetylcholine that is ultimately synthesized in the motoneuron is stored in small vesicles within the cytoplasm. It is these vesicles of acetylcholine

that are released into the synaptic cleft when an action potential arrives at the pre-junctional membrane.

Release of acetylcholine. The action potential arriving at the pre-junctional axon terminal causes depolarization of the pre-junctional membrane. This membrane depolarization, in turn, causes the transient influx of calcium ions into the axon terminal. These calcium ions cause synaptic vesicles to migrate towards and fuse with the plasma membrane, dumping their contents of acetylcholine into the synaptic cleft by exocytosis. The exact mechanism causing this migration of vesicles is not yet understood, but has been linked to calcium influx into the cell. The liberated acetylcholine quickly combines with the acetylcholine receptors on the post-junctional plasma membrane of the muscle cell causing a depolarization. The acetylcholine molecule is quickly removed from its receptor by the enzyme acetylcholinesterase. This enzyme, which exists in high concentrations in the synaptic cleft and on the post-junctional membrane, breaks down acetylcholine by hydrolysis into its component parts choline and acetate. Choline is then actively transported back into the pre-junctional axon and used to synthesize more acetylcholine (Kutchai, 1988).

Acetylcholine receptors. Acetylcholine receptors are the nicotinic type and synthesis of these receptors occurs within the muscle cell (Bowman, 1980). Acetylcholine

receptors are synthesized intracellularly from a series of protein subunits that are organized into protein cylinders and temporarily stored in the Golgi apparatus. Protein subunits are transported to and inserted through the cell's plasma membrane by an adenosine triphosphate (ATP) driven process. Once at the plasma membrane, the protein subunits are anchored into place. These protein cylinders extend from one side of the cell membrane to the other and become the acetylcholine receptors. Acetylcholine receptors extend into the junctional gap about 6 nanometers and are clustered beneath the basement membrane (Bowman, 1980). Acetylcholine receptors are made up of five subunits which are designated as alpha, beta, gamma and delta. Each receptor has two alpha subunits and one beta, gamma and delta subunit (see Figure 2). Each subunit is encoded by a

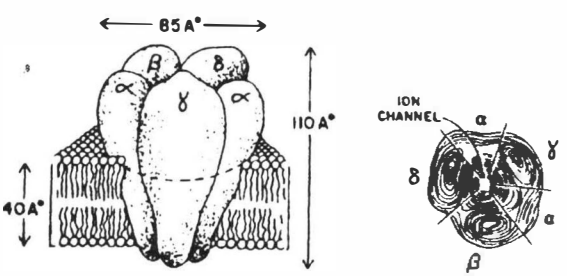

Figure 2. The nicotinic acetylcholine receptor.

Note. From "Are neuromuscular blocking agents more efficacious in pairs?" by P. Taylor, 1985, Anesthesiology, 63, p.348.

different gene, but their overall structure is very similar. Subunits are composed of chains of amino acids that are twisted into a helix and weave in and out of the plasma membrane. A greater portion of the subunit's mass protrudes from the extracellular face of the membrane than from the intracellular face (Kutchai, 1988) These subunits are held tightly together as they extend through post-junctional membrane (Standaert, 1990).

Post-junctional events. When acetylcholine is released from the pre-junctional membrane of the terminal axon, it acts as an agonist for the acetylcholine receptor binding at the two alpha subunits. Both alpha subunits must be occupied to cause a conformational change in the acetylcholine receptor. When this receptor-agonist coupling occurs, the receptor conformation changes such that a small channel between the exterior of the cell and the cytoplasm is formed. It is through this channel that selective cations (sodium, calcium, potassium and magnesium) enter the cell and cause a transient depolarization of the end plate region of the post-junctional membrane. This transient depolarization is called an end plate potential (EPP). These EPPs cause the "all or nothing" contraction of the muscle fiber by propagating the action potential around the post-junctional membrane (Bowman, 1980). The opening of the channel on the cell membrane allows the transformation of a neural chemical signal into an electrical event.

Pharmacology of neuromuscular transmission blockers. All neuromuscular transmission blocking agents resemble the molecule acetylcholine since their site of action is at the acetylcholine receptor on the post-junctional membrane. However, NTBAs differ in their mechanisms of action depending on the class of NTBA administered. There are two classes of NTBAs, depolarizing and non-depolarizing, currently used in anesthetic practice.

Depolarizing neuromuscular blockers. Succinylcholine is the only depolarizing NTBA currently in widespread use. The structure of succinylcholine is that of two connected acetylcholine molecules (see Figure 3). Succinylcholine

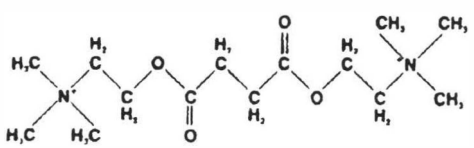

Figure 3. Structure of succinylcholine.

Note. From Clinical Anesthesia (2nd ed.) (p. 484). by D. R. Bevan and F. Donati, 1992, Philadelphia: J. B. Lippencott.

binds at the post-junctional acetylcholine receptors. This agonist receptor interaction causes a conformational change in the receptor, opening the ion channel into the muscle

cell and causing generation of an EPP. The associated EPPs cause contraction of the muscle fiber in an uncontrolled fashion due to the lack of central nervous system coordination. These uncontrolled contractions are known as muscle fasciculations (Miller & Savarese, 1990). This is the same mechanism by which acetylcholine functions, however acetylcholine's release is under neuronal regulation and coordination from the cerebral cortex and cerebellar regions of the brain. The onset of depolarizing blockade is 30 to 60 seconds and the succinylcholine molecule is not instantly broken down as is acetylcholine by acetylcholinesterase. This allows succinylcholine to hold the ion channel open, causing a continuous depolarized state. This state persists until succinylcholine is broken down by an enzyme in the blood called plasma cholinesterase. This breakdown generally occurs within 8 to 10 minutes following injection of succinylcholine. Succinylcholine causes many untoward side effects due to its structural similarity to acetylcholine and its ability to cause fasciculations. Its similarity to acetylcholine may cause parasympathetic stimulation resulting in bradycardia with nodal or ventricular escape rhythms, especially in children. Asystole has also been reported in adult patients after receiving a second dose of succinylcholine (Bevan & Donati, 1992). Fasciculations cause increased intragastric pressure, intracranial pressure, and intraocular pressure as

well as myalgias. There can be an exaggerated release of intracellular potassium into the blood. The mechanism of action for this release has not yet been established but may be attributed to the shift of potassium out of the cell when the ion channel is open during depolarization (Bevan & Donati, 1992).

Nondepolarizing neuromuscular blockers. The second class of NTBAs are non-depolarizing neuromuscular blockers. As their name implies, this class of drugs does not cause skeletal muscle depolarization. Their site of action is still the post-junctional membrane acetylcholine receptor but the interaction is one of competitive inhibition. The non-depolarizing drug molecule attaches to the alpha subunits of the acetylcholine receptor and blocks the attachment of acetylcholine. Therefore, no EPPs are created and muscle fiber contraction cannot occur. Non-depolarizing drugs may also act by blocking the pre-junctional sodium but not calcium channels (Miller, 1992). This pre-junctional block interferes with acetylcholine release from the pre-junctional membrane, further inhibiting muscle fiber contraction. Non-depolarizing NTBAs are usually comprised of bulky, rigid ring systems with a quaternary nitrogen making them ionized and water soluble (Miller, 1992) (see Figure 4). The breakdown and elimination of the nondepolarizing blockade is dependent on the specific NTBA.

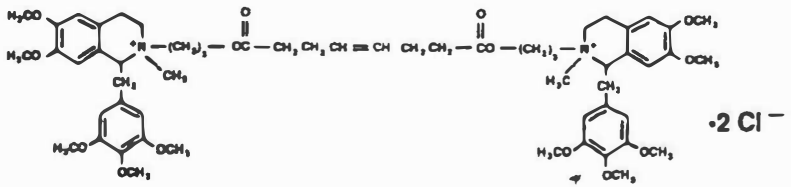

Figure 4. Non-depolarizing NTBA mivacurium chloride.

Note. From Clin ical Anesthesia (2nd ed.) (p. 492). by D. R. Bevan and F. Donati, 1992, Philadelphia: J. B. Lippencott.

Pharmacology of mivacurium chloride. Mivacurium chloride (BW B1090U, Mivacron®, Burroughs Wellcome Co., Research Triangle Park, NC 27709) is a short acting NTBA of the isoquinolinium class. It was discovered during the search for a short acting non-depolarizing NTBA to replace succinylcholine for rapid sequence inductions and short surgical procedures. At the time of mivacurium's discovery, the shortest acting non-depolarizing NTBAs were atracurium besylate and vecuronium bromide. Both of these agents are considered intermediate acting non-depolarizing NTBAs with onset times to maximal blockade of 3 to 5 minutes following injection and durations of 20 to 40 minutes. Compared to succinylcholine, their onset is much slower and their duration is considerably longer.

Mivacurium chloride offers anesthesia practitioners a more suitable alternative to succinylcholine blockade than either atracurium or vecuronium for short outpatient procedures. The time to 100% neuromuscular blockade is from 2 to 3.3 minutes monitoring the adductor pollicis with 95% recovery in 26.9 minutes (Savarese et al., 1988). During balanced anesthesia, the comparative duration of action following a single bolus dose to 95% recovery of mivacurium is approximately twice that of succinylcholine and 33-40% that of atracurium or vecuronium at similar dosages. Rapid return of neuromuscular function after mivacurium administration is due to its hydrolysis by plasma cholinesterase (Savarese et al., 1988). Infusions of mivacurium for up to 5 hours do not seem to have cumulative effects and time to recovery after discontinuation parallel those for patients receiving succinylcholine infusions (Brandom et al., 1989). Phase II block seen with prolonged succinylcholine infusions is not seen with infusions of mivacurium. A Phase II block resembles a non-depolarizing block. This change is usually the result of tachyphylaxis. The post-junctional membrane repolarizes, but does not respond normally to acetylcholine. The exact mechanism of Phase II blockade is not known (Stoelting, 1991). Unlike succinylcholine, mivacurium does not trigger malignant hyperthermia. The cardiovascular response to dosages up to two times the effective dose (ED_{95}) are minimal and are

similar to those of atracurium (Bevan & Donati, 1992). Dosages of greater than two times ED_{95} are associated with transient decreases in mean arterial pressure and increased incidence of histamine release. These adverse changes can be reduced if a dosage greater than two times ED_{95} is given in two equal divided doses, 30 seconds apart (Ali et al., 1993).

Due to the significantly longer time to onset of 95% blockade with mivacurium, succinylcholine has remained the drug of choice for rapid sequence induction of anesthesia. However, mivacurium has gained great acceptance for use in short outpatient procedures. Mivacurium is routinely used for induction of neuromuscular blockade and is often preferred for continuous infusion for short procedures.

Monitoring of neuromuscular blockade. Clinical signs to determine the onset of neuromuscular blockade (mandibular maneuverability) and amount of residual blockade (ability of the patient to sustain a head lift or protrude the tongue) are important. Ongoing assessment of physical signs of neuromuscular blockade undoubtedly help the anesthetist, but a more quantitative and reliable measurement is needed. This is especially true for the onset and intra-operative monitoring of neuromuscular blockade. During these times, the patient is anesthetized and can not follow verbal commands. It is during these times that a PNS is needed.

In 1958, Christie and Churchill-Davidscn described how the unconscious surgical patient could be assessed for neuromuscular blockade using a nerve stimulator but it was not until the middle 1960s that the peripheral nerve stimulation gained popularity (Viby-Mogensen, 1990). There have been a number of techniques developed for monitoring neuromuscular blockade using the PNS. These techniques include single twitch, tetanus, train-of-four, and double-burst stimulation of the peripheral nerve.

The single twitch response is the simplest way to elicit a neuromuscular response (see Figure 5).

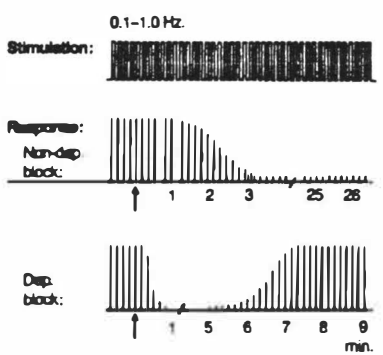

Figure 5. Pattern of electrical stimulation with evoked muscle responses to single twitch.

Note. From Anesthesia (3rd ed.) (p. 1210) by J. Viby-Mogensen, 1990, New York: Churchill Livingstone.

The twitch height of the initial, pre-relaxant twitch is assessed. Twitch height of subsequent post-relaxant neuromuscular responses are then compared to the initial pre-relaxant twitch height. Twitches can be elicited continuously from 1 to 10 seconds apart (Bevan & Donati, 1992).

Tetanus is the sustained delivery of current at 50 or 100 Hertz (Hz). This causes a sustained muscular contraction without fade in the patient who has not received NTBAs. In the presence of non-depolarizing neuromuscular blockade, tetanic stimulation shows a fade in response to stimulation. The sensitivity of tetanic response for residual blockade is greater than the single twitch response. This sensitivity increases with frequency but if 100 Hz is exceeded, some fade may be seen even in patients who have not received NTBAs (Bevan & Donati, 1992). Tetanic stimulation causes a phenomenon called post-tetanic facilitation. The large amount of acetylcholine that is released in response to a 50 or 100 Hz stimulation causes subsequent nerve stimulation to be exaggerated. This facilitation is self-limiting and twitch response usually returns to 10% of pre-tetanic values in 1 - 2 minutes following a 50 Hz stimulation of five seconds (Bevan & Donati, 1992) (see Figure 6).

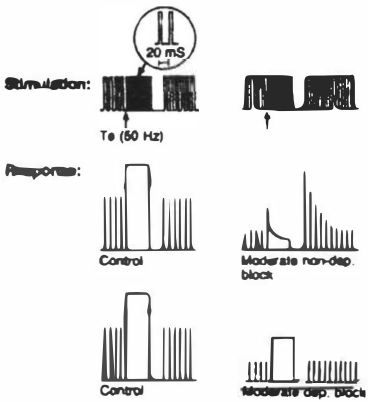

Figure 6. Pattern of electrical stimulation with evoked muscle responses to 50 Hz tetanus stimulation. Note. From Anesthesia (3rd ed.) (p. 1212) by J. Viby-Mogensen, 1990, New York: Churchill Livingstone.

Train-of-four (TOF) stimulation was first developed in 1968 as a means to better quantify neuromuscular blockade. Train-of-four stimulation employs a volley of four supramaximal stimuli at a frequency of 2 Hz over a period of 2 seconds. It is a square wave pulse not exceeding 0.2 msec. This rapid pulse is fast enough to cause the release of pre-junctional acetylcholine but slow enough to avoid facilitation (Collins, 1993) (see Figure 7).

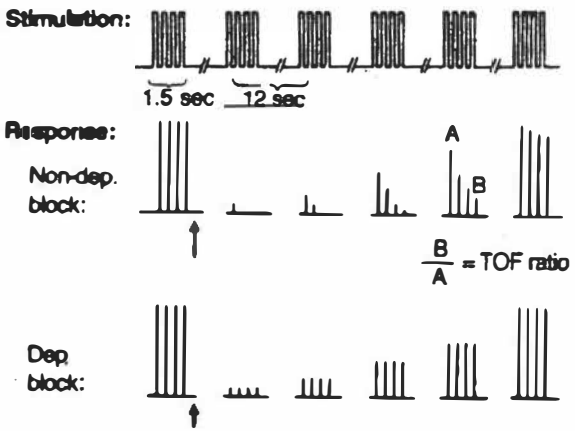

Figure 7. Pattern of electrical stimulation with evoked muscle responses to Train-of-four stimulation.

Note. From Anesthesia (3rd ed.) (p. 1212) by J. Viby-Mogensen, 1990, New York: Churchill Livingstone.

Blockade is quantified is by a comparison of the first twitch to the fourth twitch, forming a T4/T1 ratio. It has been clinically demonstrated that there is a correlation between the number of twitches suppressed and the percentage of neuromuscular blockade. Following the administration of a NTBA, the fourth twitch of the train is lost when the first twitch is 25% of control height, indicating a 75% blockade. Disappearance of the third twitch indicates a an 80% blockade with the first twitch at 20% of control. Loss of the second twitch correlates with a 90% blockade and loss of the first twitch indicates 100% neuromuscular blockade.

The presence or absence of twitches determines the depth of blockade (Collins, 1993).

Some practitioners felt that it was difficult to assess the TOF response during the recovery from neuromuscular blockade. This led to the development of double-burst stimulation. This technique consists of a train of three impulses at 50 Hz separated by 750 msec. This ratio correlates closely with the train-of-four ratio but is easier to manually detect. At least 12-15 seconds must elapse between double-burst stimulations to prevent facilitation (Bevan & Donati, 1992). All of these methods have been employed at one time or another during the development of neuromuscular monitoring by peripheral nerve stimulation. During the onset of neuromuscular blockade, train-of-four fade takes longer to develop than single twitch depression. Thus, monitoring of single twitch depression is preferred during the onset of neuromuscular blockade (Bevan & Donati, 1992). Tetanic stimulation is not useful on induction of anesthesia due to the inability to give successive stimulations less than 2 minutes apart. This is the result of facilitation caused by the massive release of acetylcholine after tetanic stimulation.

Summary

Once the choice of NTBA has been made for the induction of anesthesia and neuromuscular blockade, the anesthetist

must decide on the type of monitoring to be used during the induction and which muscle group to stimulate. Optimizing the timing from the paralysis of the vocal cords to the placement of the endotracheal tube is essential. The earlier the placement of the endotracheal tube after paralysis of the vocal cords, the less risk there is concerning gastric contents aspiration. Over the years, the discovery and use of new intermediate and short acting NTBAs and the employment of peripheral nerve stimulators has given the anesthetist more precise control over the use of neuromuscular blockade thus increasing safety.

Chapter Two

Review of Literature

Little research has been completed comparing the orbicularis oculi to the adductor pollicis muscle for monitoring neuromuscular blockade. Most studies of neuromuscular blockade involve sole monitoring of the adductor pollicis, making it the standard by which all other methods are compared. Even in the earliest days of NTBA monitoring, the adductor pollicis was selected due to its accessibility during most surgical procedures. If the adductor pollicis site was not accessible, the posterior tibial nerve was monitored. Typically the facial nerve was monitored when no other site was accessible.

Monitoring of Neuromuscular Blockade

de Jong (1966), in his classic study of neuromuscular blockade, used a "new" portable peripheral nerve stimulator to assess a surgical patient's relaxation during abdominal surgery. This study was devised to compare the strength of muscle contractions elicited in the small muscles of the hand, foot, or face from peripheral nerve stimulation with

the relaxation of the abdominal muscles. The study consisted of 65 American Society of Anesthesiologists (ASA) class I and II surgical patients between the ages of 20 and 69 years. Thirty eight women and 27 men were studied. All patients were premedicated with pentobarbital and/or meperidine and atropine or scopolamine. Each patient received a sleep dose of thiopental and an intubation dose of succinylcholine prior to endotracheal intubation. Maintenance of anesthesia was achieved with 70% nitrous oxide, 0.6% to 1.5% halothane and oxygen. Neuromuscular blockade was then induced with either decamethonium (n = 8), tubocurarine (n = 28), gallamine (n = 13) or succinylcholine (n = 16). Peripheral nerve stimulation was obtained using a battery operated PNS and needle electrodes at the ulnar (n = 52), posterior tibial (n = 9), and facial (n = 4) nerve sites. De Jong compared loss of muscle movement as measured by an electromyogram (EMG) to tactile and visual responses elicited from the PNS after administering a NTBA to 25 subjects. This allowed de Jong to correlate the near silent EMG and a "flicker" of movement from the muscle group due to peripheral nerve stimulation. This flicker of movement was at the stage of optimal surgical relaxation as judged by the surgeon. De Jong stated that the retention of 5% to 10% of muscle activity shown by the EMG was synonymous with the flicker of the muscle group monitored via the PNS.

This study was not well controlled for extraneous variables. Drug dosages, body weights, and other medications were not stated. The study was not controlled for medications that could potentiate neuromuscular blockade. The facial nerve needle electrodes were placed such that one needle pierced the parotid gland. This placement could cause the needle to be insulated, thus altering the response of the orbicularis oculi during stimulation (Wilkinson, 1988). However, time has shown that de Jong's original observations were correct. He concluded that a PNS could be substituted for the cumbersome EMG to monitor relaxation at the stated peripheral nerve sites; even though, the facial nerve was not monitored with the EMG. This was especially true at the end of the procedure when the patient was extubated and transferred to the recovery room. De Jong felt that this monitoring capability would prevent patients from being sent to the recovery room in a partially paralyzed condition.

The consistent use of train-of-four monitoring is seen in most studies involving neuromuscular blockade monitoring. Ali et al. (1985) compared train-of-four and single twitch for monitoring neuromuscular blockade during anesthetic induction and emergence. ASA class I and II patients between the ages of 18 and 59 years were studied. Each patient received morphine 0.1 mg/kg intramuscular and diazepam 0.15 mg/kg by mouth (p.o.) 1 hour prior to surgery.

Induction of anesthesia was achieved with 6 mcg/kg fentanyl and 4-8 mg/kg of thiopental. All patients were intubated using topical anesthesia without neuromuscular blockade. Maintenance of anesthesia was achieved with N_2O/O_2 at a ratio of 4L/2L respectively. A stable neuromuscular response was noted for 10 minutes and then each patient was randomly assigned to a group receiving a bolus of either atracurium 0.6, 0.1, 0.2, 0.4, or 0.5 mg/kg or vecuronium 0.02, 0.04, 0.06, or 0.1 mg/kg. The time to maximal blockade and time to 95% recovery were recorded. Half of the patients were monitored with single twitch at 0.15 Hz and the others with TOF responses at 2 Hz for 2 seconds repeated every 10 seconds. All patients were monitored employing the ulnar nerve at the wrist.

The study revealed that TOF monitoring is a more sensitive indicator for detecting the amount of neuromuscular blockade present with both atracurium and vecuronium. However, the researchers found that in all instances, single twitch was superior to TOF monitoring when assessing the patient for time to good intubating conditions. This result is also stated by Bevan and Donati (1992). They stated that the TOF fade takes longer to develop than single twitch depression thus, single twitch is preferred for monitoring onset of blockade. This study also demonstrated the converse is true for monitoring recovery from neuromuscular blockade. Single twitch consistently

returned to control levels when recovery from blockade was not greater than 75% for either NTBA. Thus the study suggested that TOF stimulation is superior to single twitch stimulation for monitoring return of neuromuscular function.

The researchers controlled for few of the variables involved with neuromuscular monitoring. Weight was not mentioned as a criteria for the selection of patients. A p-value of .05 was used for significance in this study. However, the researchers failed to give the number of patients that participated in the study. This could lead to significant error if the sample size was small. Placement of electrodes for stimulation of the ulnar nerve was not controlled and there was no mention of using templates for consistent positioning for all participants. This study revealed that different types of monitoring modalities can be utilized during different stages of neuromuscular blockade.

In 1980, Stiffel, Hameroff, Blitt and Cork used TOF stimulation while monitoring the facial and ulnar nerves. They compared use of ulnar needle electrodes to ulnar and facial surface electrodes. Fifteen ASA I, II and III patients were anesthetized with nitrous oxide, morphine and thiopental. Neuromuscular paralysis was induced with d-Tubocurarine (dTC). All patients were screened for use of aminoglycosides, acetylcholinesterase inhibitors, ganglionic blockers and magnesium. Facial surface electrodes were

placed 2 cm lateral to and 2 cm above and below the outer canthus of the eye. Ulnar surface electrodes were placed 2 cm and 9 cm proximal to the distal end of the ulna. Standard placement was achieved using cardboard templates. Ulnar needle electrodes were placed subcutaneously below the ulnar pads. The same PNS was used throughout the study. Train-of-four stimulation was elicited prior to the administration of a NTBA. All patients received 3 mg dTC and 1.5 mg/kg succinylcholine for intubation of the trachea. After recognition of the returned TOF to pre-NTBA administration, dTC was given to each patient according to the clinical judgement of the anesthesiologist. Ten minutes following the dTC injection, TOF responses were elicited and recorded sequentially at the ulnar pads, facial pads and ulnar electrodes.

Results showed a relationship between the three monitoring sites. The twitches from the TOF were seen as facial pads $\geq$ ulnar needles $\geq$ ulnar pads. The authors concluded that train-of-four responses vary considerably depending on the type and placement of electrodes. Ulnar surface electrodes give an excessive estimate of neuromuscular blockade, thus increasing the risk of inadequate muscle relaxation. In contrast, the facial pads correlated well with the ulnar needle electrodes showing an accurate picture of the degree of neuromuscular receptor occupancy by the NTBA.

The researchers in this study also failed to control for many extraneous variables. The weights and ages of the study population were not cited. Both of these factors can greatly influence the results of PNS monitoring. Excessively obese patients can have large amounts of fat deposition over the monitoring site thus increasing the distance from the skin to the stimulated nerve. This fat deposition acts as an insulator that increases the impedance for the delivered current. This may result in the nerve being submaximally stimulated and give the impression of adequate blockade. The skin of the older patient offers the same problem but in terms of decreased impedance due to thinness. There was no mention of the amount of drug used for each patient on induction, and all patients, received the same 3 mg dose of dTC. Due to the stated placement of the surface electrodes at the facial nerve site, direct stimulation of the orbicularis oculi could have occurred. This would give a misrepresentation of the actual twitches in the presence of the NMBA. The validity of this study is in question since the researchers were vague regarding controls used.

Noninvasive monitoring of the facial nerve was tested by Moore and Williams (1984). This study was to test a statement made by Savarese in a 1982 lecture suggesting that the only reliable means of assessing the facial nerve was using needle electrodes. Moore and Williams tested this

statement by using surface electrodes at the facial nerve site. Fifty patients were randomly selected from the surgical schedule. Each patient was to have general anesthesia and endotracheal tube placement. All patients were ASA class I, II, III or IV and between the ages of 17 and 81 years. Patients were selected without regard to sex or race. A single Professional Instruments Company, model NS-3a™ peripheral nerve stimulator was used with silver chloride pediatric ECG monitoring electrodes. The first electrode was placed anterior to the ear lobe, and the second was placed posterior and inferior to the same ear lobe. Tetanus, twitch and TOF stimulation were used to assess neuromuscular blockade. The study revealed that 94% of the patients had observable twitches at the orbicularis oris, orbicularis oculi or zygomaticus major muscles. The researchers failed to state the type of stimulation the patients received and the outcome of each type. There was also a lack of information on 6% of patients that did not have observable twitches. However, this research demonstrates a high degree of success for stimulating the facial nerve without the use of needle electrodes.

Comparison of Various Muscle Group Responses to Neuromuscular Stimulation

Caffrey, Warren and Becker (1986) were one of the first groups that directly compared facial nerve stimulation to

ulnar nerve stimulation during neuromuscular blockade. The study consisted of nine ASA I or II patients between the ages of 26 and 78 years. Patients that were markedly obese or had underlying neuromuscular disease were excluded from the study. All patients received 25 mg meperidine, 2.5 mg diazepam and 0.2 mg atropine as a premedication. Induction of anesthesia was achieved with 5 mg/kg thiopental and 1.5 mg/kg succinylcholine. Intubation of the trachea was achieved and thumb twitch height was allowed to return to pre-relaxant levels. Anesthesia was maintained with enflurane 2.0 - 2.5% and 50% N_2O/O_2. Atracurium was titrated to loss of a single twitch and loss of tetanic response to stimulation at the facial and ulnar sites. Patients were then allowed to recover from the NTBA while being monitored with the TOF technique. Orbicularis oculi and adductor pollicis responses to stimulation were assessed with linear force transducers.

The study showed that the first and fourth twitch at the facial nerve site consistently returned to pre-NTBA levels before the ulnar nerve site. However, when the TOF returned to normal levels at the facial nerve site, considerable weakness was still apparent as tested by the sustained head lift technique. Train-of-four response at the ulnar nerve site at the same time showed significant fade. Caffrey et al. (1986) concluded that the facial nerve response returns prior to the ulnar nerve response and there

was less chance of residual neuromuscular blockade if the ulnar site was assessed for reversal of NTBA blockade.

This study controlled many of the variables associated with neuromuscular blockade monitoring. The number of patients studied was small, but results were consistent and significance was evaluated at a $p < .05$. Placement of electrode patches was generalized, therefore the risk of direct muscle stimulation at the orbicularis oculi was increased. This study did not compare ulnar and facial nerve stimulation on induction of neuromuscular blockade. However, the results showed that the facial nerve was a more sensitive indicator for assessing the return from neuromuscular blockade during the intra-operative period. The authors suggested that the anesthetist should use caution when monitoring the facial nerve response to stimulation for extubation criteria.

Campbell (1989) compared the facial and ulnar nerve response during vecuronium neuromuscular blockade. The times to onset and recovery of response to blockade were recorded in 13 ASA I and II patients. All patients were between 18 and 54 years of age and were not obese. All patients were free from neuromuscular disease and presented for surgery in sites other than the face or upper extremities. These patients were divided into one of two groups as follows: Group 1 was given a dose of 0.1 mg/kg vecuronium and Group 2 was given 0.5 mg/kg vecuronium to

induce muscle relaxation after induction of anesthesia. Induction of anesthesia was achieved with thiopental 3-5 mg/kg and fentanyl 2 mcg/kg. Anesthesia was maintained with 0.5 - 1.5% isoflurane and 50% nitrous oxide. The two groups were stimulated with the TOF modality every 2 minutes following intubation and every 2 minutes until recovery of one muscle group was demonstrated. At that point, the sites were monitored more frequently until the TOF was evident in both muscle groups. Placement of electrodes at the facial and ulnar sites were consistent using a cardboard template and as indicated by Stiffel et al. (1980). Baseline TOF twitch responses were recorded prior to neuromuscular blockade and each patient served as their own control. Both muscle groups were stimulated and monitored simultaneously. Simultaneous stimulation was achieved by using a single nerve stimulator equipped with two sets of electrode leads.

Results obtained from Group 1 revealed that after 2 minutes, all hand responses evidenced 100% blockade while the face showed four responses to stimulation. In Group 2, neuromuscular blockade took longer to develop due to the smaller dose of vecuronium. At 4 minutes, the hand showed 100% blockade and the face showed two to four responses to stimulation. The TOF recovery from vecuronium blockade was significantly earlier at the face than at the hand.

The researcher concluded that the facial neuromuscular response was more resistant to and recovered earlier from

vecuronium blockade than the ulnar neuromuscular response. The explanation offered was a difference in the contribution of Type I and Type II muscle fibers that make up the orbicularis oculi and the adductor pollicis groups. The statement was also made that the extraocular and facial muscles have a proportionately larger number of neuromuscular junctions as compared to other muscles of the body and are more difficult to ablate with NTBAs.

Unfortunately, there was no mention of control for the amount of current delivered to each of the two monitored nerves. A single nerve stimulator delivers a constant current over a specified range of impedances. However, the stimulator used by the researcher had two sets of leads. This would cause the delivered current to be split between the two parallel circuits created when attaching the two sets of positive and negative electrodes. There is considerable difference in the impedance at the facial nerve where the two poles are 3 centimeters (cm) apart and the ulnar nerve where the poles are 7 cm apart. A proportionately higher amount of the current delivered by the PNS follows the path of least resistance which is at the facial nerve electrodes. This results in the facial nerve being supramaximally stimulated and the ulnar nerve being submaximally stimulated. This difference in the amount of current delivered for stimulation could account for the loss of response at the ulnar site prior to the facial site.

Donati, Meistelman and Plaud (1990) studied the relationship between the diaphragm, orbicularis oculi and the adductor pollicis muscles with vecuronium neuromuscular blockade. Sixteen adult patients scheduled for laryngeal and pharyngeal endoscopy were selected. Patients with respiratory, cardiovascular and neuromuscular disease were excluded from the study as were patients with excessive alcohol intake and current administration of medications affecting neuromuscular function.

The first group received 0.07 mg/kg vecuronium and the second group received 0.04 mg/kg vecuronium for muscular paralysis. Preoperative diazepam 5 - 10 mg was given to all participants 1 hour prior to scheduled surgery. Anesthesia was induced with intravenous alfentanil 20 - 30 mcg/kg and propofol 2-3 mg/kg. Endotracheal intubation was achieved without the use of NTBAs. Anesthesia was maintained with a propofol infusion at 10 mg/kg/hr with intermittent doses of alfentanil. Surface electrodes were applied to the ulnar nerve at the wrist, to the right phrenic nerve at the base of the neck and the temporal branch of the right facial nerve, anterior to the ear lobe. The response to the PNS was measured at the adductor pollicis with a force transducer. The responses from the orbicularis oculi and the diaphragm were measured via an electromyograph. Supramaximal stimulation was achieved at all three monitored sites prior to the administration of vecuronium.

Supramaximal TOF stimulation was delivered every 10 seconds to all three sites and baseline responses were recorded for 2 - 3 minutes. Vecuronium was then given at 0.4 mg/kg for eight patients and 0.7 mg/kg for the other eight patients. Times to 5%, 50% and maximum T_1 blockade were made as well as 25% and 75% T_1 recovery. The T_1 response of the orbicularis oculi and the adductor pollicis were plotted against the T_1 response of the diaphragm for onset and recovery from vecuronium blockade.

In both groups, onset and recovery from NTBA blockade was more rapid in the diaphragm than at either the adductor pollicis or the orbicularis oculi muscles. When comparing the adductor pollicis to the orbicularis oculi, the neuromuscular blockade at the orbicularis oculi was only slightly slower than the diaphragm whereas, the adductor pollicis blockade took significantly longer to develop. Maximal blockade occurred in the diaphragm at 2.9 minutes, at the orbicularis oculi at 3.8 minutes and at the adductor pollicis at 6.8 minutes with a vecuronium dose of 0.04 mg/kg. The vecuronium dose of 0.07 mg/kg showed almost identical results. Recovery from neuromuscular blockade was fastest at the diaphragm, followed by the orbicularis oculi and the adductor pollicis. Donati et al. (1990) stated that the amount of NTBA required to cause a 90% blockade at the diaphragm is 40 to 100% greater than that required for blockade at the adductor pollicis. However, diaphragmatic

paralysis occurs and resolves sooner due to differences in blood flow and early distribution of the relaxant. The researchers stated that the stimulation of the phrenic nerve during surgery is impractical and that the orbicularis oculi should be used since it most accurately reflects the amount of paralysis at the diaphragm. The researchers controlled for many variables of neuromuscular blockade monitoring and the drug dosages were controlled on a milligram or microgram per kilogram basis. The number of subjects was small but the results were consistent ($p = .01$).

Donati, Meistelman and Plaud (1991) continued their research of neuromuscular blockade when they compared vecuronium neuromuscular blockade at the adductor pollicis and the adductor muscles of the larynx. Twenty ASA I or II adult females were selected for the study. Patients with abnormal airway exams, cardiovascular, respiratory, hepatic and renal disease, previous head and neck surgery or chemotherapy known to interfere with neuromuscular function or blockade were excluded from the study. Upon arrival to the operating room, baseline ECG, pulse oximetry, and arterial blood pressure were monitored. Induction of anesthesia was achieved with propofol 2-4 mg/kg, and fentanyl 2-5 ug/kg. An endotracheal tube was placed with direct visual laryngoscopy placing the cuff between the vocal cords without use of an NTBA. End tidal carbon dioxide ($ETCO_2$) was held constant between 35-40 mmHg and

anesthesia was maintained with propofol and fentanyl. Nitrous oxide and halogenated agents were avoided. The adductor pollicis was stimulated by placing skin type ECG electrodes at the ulnar nerve site at the wrist. Stimulation of the recurrent laryngeal nerve was achieved by placing the negative electrode on the skin overlying the notch of the thyroid cartilage, with the positive electrode on the sternum or the forehead. Adductor pollicis movement was recorded using a force transducer. The vocal cord response was monitored by fluctuations in the endotracheal tube cuff pressure and recorded with a chart recorder. Neuromuscular blockade was induced using 0.4 mg/kg in 10 of the patients and 0.7 mg/kg in the remaining 10 patients. Supramaximal TOF stimulations were applied to both sites to obtain a baseline response. Induction of blockade was measured using TOF pulses at 10 second intervals. Onset time was defined as the interval between the time of injection to maximal T_1 blockade.

Maximal blockade was less intense at the vocal cords than at the adductor pollicis at both dosages. In all 20 participants, onset was faster and recovery was earlier at the vocal cords than at the adductor pollicis. The researchers concluded that there are important differences in the laryngeal muscles and the adductor pollicis with regards to their response to vecuronium. They also stated that a possible explanation for the differences in

resistance and speed of onset was due to differences in muscle fiber tissue types. They cited that experimental data revealed that fast twitch muscles were more resistant to neuromuscular blockade. The laryngeal muscles were made of fast contracting fibers unlike those of the slow contracting adductor pollicis muscles. The suggestion was also made that the faster onset of the blockade at the vocal cords, as in the diaphragm, was due to blood flow. Therefore, assessment for optimal time to intubation should be governed by a fast twitch muscle like the orbicularis oculi.

The researchers controlled for many variables but only female subjects were studied. There was also a lack of control for lead placement at the ulnar nerve, thus direct muscle stimulation could have occurred. The results were consistent at a p value $\leq .05$, thus adding validity to the study.

The method of neuromuscular blockade monitoring can be as varied as the site chosen for stimulation. Little research has been focused on considering both the method and the site for assessing optimal intubating conditions of the vocal cords. Donati et al. (1990) demonstrated that the onset of neuromuscular blockade at the diaphragm and orbicularis oculi muscle precede that of the adductor pollicis. Donati et al. (1991) demonstrated the onset of neuromuscular blockade at the laryngeal muscles correlated

well with the onset times for the diaphragm and orbicularis oculi (see Figure 8).

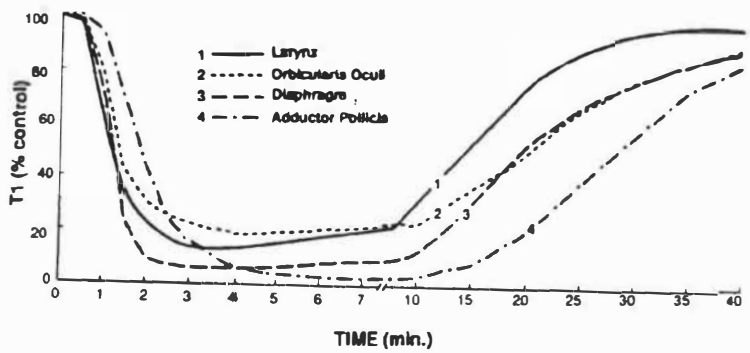

Figure 8. Onset and recovery after vecuronium, 0.07 mg/kg at various muscles vs. time.

Note. From Clinical Anesthesia (2nd ed.) (p. 499). by D. R. Bevan and F. Donati, 1992, Philadelphia: J. B. Lippencott.

Therefore, monitoring the orbicularis oculi muscle using single twitch stimulation should provide the anesthetist with the earliest signs of optimal intubating conditions.

Iwasaki, Igarashi, Omote and Namiki (1994) studied the sensitivity of the cricothyroid (CT) and posterior cricoarytenoid (PCA) muscles to vecuronium induced neuromuscular blockade. Nine ASA I and II patients undergoing surgery for total laryngectomy for unilateral laryngeal cancer were selected to participate in the study.

All patients received atropine 0.5 mg IV and midazolam 2.5 mg intramuscularly 1 hour prior to induction of anesthesia. A sleep dose of thiamylal, 4 - 5 mg/kg and fentanyl 3 - 5 mcg/kg was given. Succinylcholine 1 mg/kg was given to aid endotracheal intubation. Anesthesia was maintained using additional fentanyl, midazolam and 66% N_2O with 34% O_2. The Halogenated agents were avoided to prevent potentiation of the neuromuscular blockade.

Surgical exposure facilitated the placement of stainless steel electrode leads into the superior laryngeal and recurrent nerves on the unaffected side. This placement provided indirect stimulation of the CT and PCA muscles. Stimulation was achieved using pulses of 0.2 millisecond duration every 10 seconds at 1.4 to 12 mA. Twitch height following stimulation was measured using an EMG for the muscles of the larynx and a mechanomylogram at the adductor pollicis for 5 minutes. Once stable baseline recordings were established, vecuronium was continuously infused at a rate of 0.01 mg/kg/min for 10 minutes. Recordings of the twitch height depression were made and compared.

The results of the study revealed that the intrinsic laryngeal muscles did not behave similarly with vecuronium induced neuromuscular blockade. In all cases, the CT and adductor pollicis muscles were clearly more sensitive to vecuronium neuromuscular blockade than the PCA muscle. The recovery from neuromuscular blockade was not monitored.

The researchers did not control for many of the variables affecting neuromuscular blockade such as weight and pre-existing neuromuscular disease which could lead to erroneous results. The small number of patients in the study could also have lead to false conclusions. However, 100% of the patients had the same results which helps to lend some validity to this study.

Mivacurium Chloride

Savarese et al. (1988) investigated the neuromuscular blocking properties of mivacurium chloride to include potency, dose-response relationships for onset and duration and reversibility with neostigmine. Seventy-two ASA physical status I and II patients, between the ages of 18 and 49 years, were studied. Patients with preexisting neuromuscular, cardiovascular, renal or hepatic disorders were excluded. All patients received intramuscular morphine (0.1-0.15 mg/kg) and/or diazepam (0.1-0.2 mg by mouth) 1 hour preoperatively. All patients had radial arterial cannulae placed for blood pressure monitoring. Anesthesia was induced using thiopental (4-8 mg/kg) and fentanyl (4-8 mcg/kg) IV. Nitrous oxide and oxygen (4L/2L inspired mixture) were delivered via face mask. Intubation of the trachea was achieved without muscle relaxant by using topical lidocaine. Blood pressure and heart rate were measured at 1 minute intervals for 5 minutes before and 10

minutes following the injection of mivacurium. The single twitch of the thumb was evoked at 0.15 Hz using square wave pulses 0.2 msec in duration at the ulnar nerve with needle electrodes. Train-of-four stimulation (2 Hz for 2 sec) was applied at 5-10 minute intervals during maintenance and recovery from neuromuscular blockade. Adduction of the thumb was quantified with a force-displacement transducer. The results of the study showed that 0.1, 0.15, 0.2, 0.25 and 0.3 mg/kg of mivacurium given as a single dose resulted in a mean time to 95% twitch recovery of 25.3, 25.1, 27.9, 30.1 and 29.9 minutes and a mean time to T_4 > 70% of 28.7, 28.9, 30.8, 32.2 and 31.6 minutes respectively. Savarese et al. (1988) also showed that the molar potency ratio of mivacurium was similar to vecuronium and pancuronium and almost three times that of atracurium. However, multiple doses of up to three times mivacurium's ED_{95} only prolonged the neuromuscular blockade by 5 to 10 minutes. This disproportionate increase in dose to a small extension of duration of effect is unlike any other non-depolarizing neuromuscular blocker.

The hydrolysis of mivacurium by plasma cholinesterase was also studied with regard to the effects of reversal with the anticholinesterase neostigmine. At the conclusion of the study, eight patients were reversed with neostigmine. Savarese et al. (1988) found that reversal of the neuromuscular blockade did not potentiate the neuromuscular

blockade from mivacurium. However, the induced recovery only preceded the spontaneous recovery by 4 minutes.

The study by Savarese et al. (1988) was one of the first conducted measuring the pharmacodynamics of mivacurium. The study was well controlled for medical conditions that could potentiate neuromuscular blockade. The large sample size could provide statistical significance however, there was no mention of confidence intervals or levels of significance throughout the article. Ulnar needle electrodes reduced skin impedance to electrical nerve stimulation, but exact placement of the electrodes was not specified other than at the wrist.

Savarese et al. (1989) continued their studies of mivacurium chloride. This study focused on the cardiovascular effects of mivacurium and looked specifically at heart rate, blood pressure and histamine release at various dosages of mivacurium. Ninety-seven ASA physical status I and II patients of both sexes between the ages of 18 and 49 years with weights ranging from 50 to 100 kg were studied. Patients with preexisting neuromuscular, cardiovascular, renal or hepatic disorders were excluded. All patients were given intramuscular morphine (0.1-0.15 mg/kg) and diazepam by mouth (0.1-0.2 mg/kg). All patients had a 20 gauge arterial catheter placed to monitor blood pressure. Induction of anesthesia was achieved using thiopental (4-8 mg/kg) and fentanyl (4-8 mcg/kg) IV.

Nitrous oxide and oxygen (4L/2L inspired mixture) was delivered via face mask. Intubation of the trachea was achieved without muscle relaxant by using topical lidocaine. After obtaining a stable baseline of heart rate and blood pressure for 10 minutes mivacurium was injected over 10 to 15 seconds. During injection of mivacurium at ED_{95} and above, direct arterial pressure and heart rate were continuously recorded. Twitches were evoked by stimulation of the adductor pollicis at 0.15 Hz and were continuously recorded. Cardiovascular responses were recorded for 10 minutes after injection or until blood pressure and heart rate returned to 95% of control levels. Mivacurium dosages given ranged from 0.03 to 0.3 mg/kg. Three additional groups of nine patients were given the same dosages as above but over a longer 30 to 60 second injection time. Plasma histamine levels were assayed after all doses greater than ED_{95}. Arterial blood samples were drawn immediately before, and at 5 minute and 10 minute intervals following the mivacurium injection. The incidence of decline of mean arterial pressure less than (<) 80% of control did not occur in the groups receiving 0.1 or 0.15 mg/kg of mivacurium given as a bolus over 10 to 15 seconds. However, the group receiving 0.15 mg/kg mivacurium had a 33% incidence of increased serum histamine release greater than (>) 1,000 picograms/ml of blood. Dosages greater than 0.15 mg/kg mivacurium also resulted in equivalent histamine release and

decline of mean arterial pressures > 80% of control values. The only exception was the group given 0.25 mg/kg injected over a 60 second time period where the results were similar to the 0.1 mg/kg dosage group.

This study demonstrated that mivacurium's effects on the cardiovascular system were significant at dosages greater than 2 X ED_{95} when given over 10-15 seconds. The authors attributed the cardiovascular effects to the histamine release as shown earlier. However, Savarese et al. (1989) also found that a second administration of mivacurium over 10-15 seconds only decreased the blood pressure and heart rate to 98 and 92% of control values.

The large number of participants in this study and the controls for neuromuscular disease added confidence in the exhibited results. Savarese et al. (1989) also used a p-value of .05 to indicate significance. A lack of description of lead placement for neuromuscular blockade was not detrimental to the study results in that the focus was on specific dosages of mivacurium and responses of the cardiovascular system, not the amount of neuromuscular blockade.

Brandom et al. (1989) devised a study to compare mivacurium and succinylcholine administered by bolus and infusion. Thirty ASA I and II patients between the ages of 18 and 57 years were studied. Women of child bearing age were excluded as well as patients receiving aminoglycoside

antibiotics or antihistamine drugs. All patients received diazepam 0.1-0.2 mg/kg by mouth and or intramuscular morphine 0.05-0.1 mg/kg 1 hour prior to induction. Blood samples were drawn to measure plasma cholinesterase activity and dibucaine number. Induction of anesthesia was achieved with thiopental 3-5 mg/kg and fentanyl 1-6 mcg/kg and maintained with 70% nitrous oxide and 30% oxygen. The ulnar nerve was stimulated with repeated TOF via surface electrodes at the wrist. Measurements of supramaximal and continuous twitch response were obtained using an EMG of the adductor pollicis.

The percent of neuromuscular blockade was calculated from the amplitude of the first TOF responses (T1) after bolus administration to the T1 before drug administration. After the infusion was stopped, recovery was determined from the first stable T1 response to a TOF ratio (T4-T1) that was greater than 0.9. Tracheal intubation was attempted 60 seconds after succinylcholine and 90 seconds after mivacurium administration. Intubation was attempted at the specified time interval if 80% neuromuscular blockade had been achieved. If neuromuscular blockade was not greater than 80% at the time interval specified, intubation was postponed until 80% blockade was achieved. Conditions of intubation were graded as excellent (no resistance to laryngoscopy, no movement of vocal cords); good (same as excellent but some coughing); fair (no resistance to

laryngoscopy but movement of the cords and coughing); poor (intubation could not be performed). Infusions of succinylcholine and mivacurium were started with the return of one twitch response of the TOF. Infusions were stopped at the end of the procedure and patients were monitored for recovery of neuromuscular function. The times between cessation of infusion and recovery to 5% (T5), 25% (T25), 50% (T50), 75% (T75), and 95% (T95) of baseline were noted.

All patients developed complete neuromuscular blockade from the bolus dose of succinylcholine 1 mg/kg. Twelve of the 14 patients receiving mivacurium 0.25 mg/kg exhibited complete neuromuscular blockade. The two patients not obtaining complete neuromuscular blockade were excluded from the study.

The study revealed that the onset of neuromuscular blockade was significantly shorter for succinylcholine than that for mivacurium. Most patients receiving the 0.25 mg/kg bolus of mivacurium did develop facial and truncal flushing. The recovery indices (T25-T75) after infusions of succinylcholine and mivacurium were approximately 6 minutes. The recovery index for mivacurium after a bolus dose was also about 6 minutes.

The controls for this study were poorly executed. Lack of a specific placement of electrodes for eliciting neuromuscular response can lead to many erroneous results. There was no mention of a control for patient weight which

can also lead to error due to altered conduction of peripheral nerve stimulation. It was impossible to ascertain why two patients failed to obtain complete neuromuscular blockade. The number of patients was sufficient for providing confidence in the results with a stated $p < .05$.

Mivacurium chloride has been shown to have a predictable and consistent hemodynamic and pharmacologic profile. When mivacurium is administered at 2 X ED_{95}, it has an onset time between 90 and 180 seconds which is comparable to the widely used NTBAs atracurium and vecuronium. Mivacurium's advantage is seen in its rapid hydrolysis and elimination which is almost half the time required for vecuronium or atracurium. This makes mivacurium preferable for short and intermediate length surgical procedures. Reversal of mivacurium's neuromuscular blockade may not be necessary thus making it ideal for outpatient procedures where the incidence of nausea and vomiting may increase if a anticholinergic is used for reversal. Unfortunately, mivacurium's onset time for neuromuscular blockade is inferior to that of succinylcholine thus precluding its use for rapid sequence intubation.

Chapter Three

Methodology

Research Design

The design for this study was quasi-experimental. An experimental design was not feasible and a control group was not used since each person served as his/her own individual control. This study compared the relationship between the facial and ulnar nerve-mediated response to neuromuscular blockade with mivacurium chloride during intubation. Patients were chosen as they presented for surgery and met the population inclusion criteria for the study.

Population and Sample

Twenty ASA class I and II male and female adults between the ages of 18-65 years, with body weights between 45-100 kg requiring general anesthesia with neuromuscular blockade were selected for study. Those patients with known peripheral neuropathies associated with diabetes, myasthenia gravis, myotonia and muscular dystrophy were excluded from the study along with patients receiving any medication that potentiates NTBA blockade.

Setting

This study was conducted at a large tertiary care medical facility. The data was collected over a period of 8 weeks.

Data Collection Procedure

All patients participating in the study were given premedication of 2 mg of midazolam IV. Upon arrival to the operating room, routine monitors were connected and baseline blood pressure, pulse and respirations were recorded with subsequent recordings at 5 and 10 minutes following induction of anesthesia.

Indirect stimulation of the ulnar nerve was achieved by placing commercially available silver chloride ECG electrodes 2 cm and 10 cm proximal to the distal end of the ulnar nerve. Placement of the electrodes at these sites should have avoided any direct muscle stimulation of the adductor pollicis and elicited an indirect stimulation via the deep branch of the ulnar nerve (Wilkinson, 1988). The same type of ECG electrodes were used to monitor the orbicularis oculi muscle group. The first electrode was placed 2 cm lateral and 2 cm caudal to the outer canthus of the eye and the second 2 cm caudal to the first. This placement avoided direct stimulation of the orbicularis oculi and maximized stimulation indirectly via the facial nerve. Each site selected for lead placement was cleaned

with alcohol pledgets prior to placement to remove any excess oils which could cause increased impedance. The leads were placed on the same side of the body for monitoring the orbicularis oculi and the adductor pollicis.

Induction of anesthesia was achieved with 0.1 mg/kg IV of mivacurium followed by 100 mcg of fentanyl IV and 2 mg/kg IV of propofol. The second dose of mivacurium 0.1 mg/kg was administered 30 seconds after the initial dose. Baseline twitch response was immediately started at both monitoring sites using 1 Hz twitch per second mode with an output of 60 mA. Each patient was simultaneously monitored until there was a loss of twitch response at either of the two sites. When the twitch response had been suppressed at one site, the anesthetist performed direct visual laryngoscopy. If the vocal cords were relaxed and open, the trachea was intubated. If the vocal cords were not relaxed, the anesthetist withdrew the laryngoscope and waited for the suppression of the second monitoring site. After successful tracheal intubation, the anesthetist charted the time the second 0.1 mg/kg dose of mivacurium was given, the time the first twitch was suppressed and at which monitoring site, whether the vocal cords were open or closed, if the trachea was intubated, and the time the second monitoring site twitch suppression was achieved. If the trachea was not intubated with the loss of the twitch response at the first monitoring site, the time and relaxation of the vocal cords

would be recorded with the laryngoscopy following the loss of the twitch response at the second monitoring site. The anesthetist also recorded the side of the body used for peripheral nerve stimulation and if there was evidence of histamine response monitored by facial or truncal flushing.

Instrumentation

The Fischer and Paykel NS252 peripheral nerve stimulator is a fully programmable solid state battery powered instrument designed for monitoring peripheral neuromuscular blockade. It utilizes three 1.5 volt AAA batteries to deliver the power to the pulse generator. The pulse generator disburses a square wave pulse 200 microseconds (+/- 5 microseconds) in duration with an output rise/fall time of less than 5 microseconds using the single twitch mode at 1 Hz. The maximum load impedance for single twitch is 4 kilo-ohms at 80 milliamperes (mA) and the ability to generate a maximum output of 350 volts. The manufacturer specifications are maintained for a minimum of 300 hours of use with newly charged alkaline batteries. If battery failure should occur, audio alarm and liquid crystal display (LCD) are activated to inform the user. In addition, the LCD continuously displays the current to be delivered in mA. If the set current is not delivered due to a disconnected lead, excessive impedance, or dry electrode patches, a fault symbol and audio alarm are initiated. The

ability to adjust and set the output current is achieved by pressing membrane touch switches. There are 14 switches in all used for setting functions as well as turning the stimulator on and off. The output current used for this study was preset at 60 mA delivered by a single twitch at 1 Hz which is sufficient to cause supramaximal twitch response.

Statistical Analysis

Data collected from the study was examined using a paired t-test and a comparison of the mean times to loss of twitch at the orbicularis oculi and the adductor pollicis was made. The paired t-test was selected due to the measurement of two variables in the same individual with each subject acting as his own control. The mean change in heart rate at 5 and 10 minutes after injection of mivacurium, the mean change in blood pressure at 5 and 10 minutes after injection of mivacurium, age, weight, sex and ASA classification were compared to the loss of twitch at the orbicularis oculi and the adductor pollicis using regression analysis and scatter plots to ascertain any significance in the relationship among these variables. The level of significance was set at a $p < .01$.

Informed Consent

A waiver of informed consent was obtained from the University institutional review board. The waiver was granted due to the use of medications, dosages and monitoring techniques that fall within the standard of care for anesthetic practice.

Chapter Four

Results

Sample Population

The 20 patients studied had a mean age of 36 years with the youngest being 15 years and the oldest 64 years. This sample population was made up of five females (20%) and 15 males (80%). The mean weight of the sample was 76.6 kg ranging from 45 kg to 100 kg. Neuromuscular stimulation response was obtained on the left side of the body in 5 (20%) subjects and on the right side of the body in 15 (80%) of the subjects. The orbicularis oculi and adductor pollicis were monitored exclusively on one side in each subject. All patients were also monitored for histamine response as demonstrated by facial or truncal flushing and for movement during laryngoscopy.

Comparison of the Loss of Twitch Response

All 20 of the subjects had a loss of the orbicularis oculi motor response to stimulation prior to the loss of motor response to stimulation at the adductor pollicis. The minimum time to loss of twitch response at the orbicularis

oculi was 55 seconds with a maximum of 152 seconds and a mean of 85.45 seconds. The variance was shown to be 779.31 seconds with a standard deviation of 27.91 seconds. The minimum time to the loss of twitch response at the adductor pollicis was 149 seconds with a maximum of 435 seconds and a mean of 230.25 seconds. The variance was found to be 5,786.93 seconds and a standard deviation of 76.07 seconds. In all subjects, the loss of the twitch at the orbicularis oculi occurred first and laryngoscopy was performed. All 20 of the subjects had visible, open, immobile vocal cords through which an endotracheal tube was passed. One subject showed movement during placement of the endotracheal tube. The time to loss of the twitch response at the orbicularis oculi was subtracted from the time to loss of the twitch response at the adductor pollicis for each patient. This resulted in a minimum difference of 73 seconds and a maximum difference of 283 seconds with a mean difference of 144.80 seconds. All of the patients exhibiting longer times to loss of twitch response in the arm and face were males and had an ASA classification of II.

Comparison of Cardiovascular Response

The arterial systolic and diastolic pressure of each subject was obtained using non-invasive blood pressure monitoring. A baseline blood pressure was obtained prior to induction of neuromuscular blockade and anesthesia, as well

as, 5 minutes and 10 minutes after induction of general anesthesia had occurred. The mean arterial pressure (MAP) was derived by the addition of the systolic pressure and twice the diastolic pressure and dividing the sum by 3 for each subject. The baseline MAP ranged from 68 to 126 mmHg with a mean of 90.4. At 5 minutes, the MAP has a wider range than the baseline MAP at 43.7 to 145.7 mmHg, but the mean MAP at 5 minutes was lower than the baseline at 85.9 mmHg. The mean MAP at 10 minutes was lower than both the baseline and 5 minute mean MAP at 80.1 mmHg. The MAP standard deviation at 5 minutes and 10 minutes was greater than the MAP standard deviation at the baseline as well. Three subjects out of the 20 had declines of greater than 20% of their baseline MAP at the 5 minute measurement and six patients had a greater than 20% decline in their MAP at the 10 minute measurement. One subject out of the 20 had an increase in MAP greater than 20% of the baseline at the 5 minute measurement.

The heart rate measurements were obtained from a five lead electrocardiogram (EKG) monitor placed on each subject and recorded prior to induction of neuromuscular and anesthetic induction and at 5 minute and 10 minute time periods. The mean heart rate measurements show little variation between the three monitored times. The lowest mean heart rate was 73.5 at baseline and the highest was 82.7 at the 5 minute time period.

Chapter Five

Discussion

Discussion of Twitch Response

The statistical analysis of the data provided significant evidence that a difference exists between the time to loss of twitch response at the orbicularis oculi and the adductor pollicis muscles. Therefore, the null hypothesis was rejected. This statement was supported by the fact that 100 % of the study subjects lost the mean twitch response (MTR) at the orbicularis oculi 144.8 seconds prior to the loss of the MTR at the adductor pollicis.

These results were in agreement with the work of Donati et al. (1990) who showed that the smaller muscles of the orbicularis and the larynx succumb to neuromuscular blockade before the larger muscles of the adductor pollicis. According to the work of Johnson et al. (1973), 90 % of the orbicularis oculi muscle is composed of fast contracting, Type II muscle fibers. The adductor pollicis is composed primarily of slow contracting, Type I muscle fibers. Differences in muscle fiber type may explain some of the differences in the time to the loss of twitch response at

these two monitored sites. Claassen and Werner (1992) studied the muscle fiber composition of the larynx. Their results demonstrated that the muscles responsible for the adduction of the vocal cords (lateral cricoarytenoids, cricothyroid) are primarily composed of Type II muscle fibers whereas the abductor (posterior cricoarytenoid) is primarily composed of Type I muscle fibers. If the muscle fiber type was responsible for the differences in the loss of MTR at the orbicularis and adductor pollicis, the same should hold true for the laryngeal muscles. The results obtained in the study helped to confirm this postulate by virtue of the vocal cords being open for each laryngoscopy attempted at the loss of twitch response at the orbicularis oculi. Donati et al. (1991) studied the onset of neuromuscular blockade at the larynx, diaphragm and adductor pollicis. These researchers found that the paralysis of the laryngeal muscles and the diaphragm precede the adductor pollicis. The diaphragm, however, is predominantly composed of Type I muscle fibers. This seemingly contradicted the postulate that time of onset of neuromuscular blockade was due to muscle fiber type. The explanation for this may be preferential blood flow to the diaphragm. This preferential blood flow allows a greater amount of the NTBA to reach the muscle fibers of the diaphragm before the equivalent amount reaches the adductor pollicis. This large concentration shortens the time to 100% twitch depression (Miller, 1985).

Iwasaki et al. (1994) directly measured the response of muscle stimulation using EMG at the CT and PCA muscles during the onset of neuromuscular blockade. The results obtained found that the PCA (predominantly Type I) muscle, is more resistant and takes longer to develop 100% neuromuscular blockade than does the CT muscle (predominantly Type II). Therefore, paralysis of the CT muscle allows unopposed abduction of the vocal cords by the PCA muscle.

The results from this study also showed that the time to loss of MTR in males were longer than in females. The size of the sample population and the fact that only 20% of the sample population was female may have contributed to this result. A larger sample population may very well revealed that no difference exists based on sex.

Discussion of Cardiovascular Results

The facial and truncal erythema exhibited by one subject and the decline of >20% of baseline MAP of three subjects at the 5 minute interval and six subjects at the 10 minute interval, are somewhat higher than previous studies have shown for a single dose of 0.1 mg/kg mivacurium, but lower than a single dose of 0.2 mg/kg mivacurium. Savarese et al. (1989) revealed a decline of >20% in baseline MAP in 0/9 subjects studied given a bolus of 0.1 mg/kg mivacurium and 4/9 subjects given the 0.2 mg/kg mivacurium bolus.

Savarese et al. (1989) controlled for variables that could cause a decline of MAP such as the induction dose of thiopental and the use of volatile anesthetics. Intubation was achieved without muscle relaxant and a consistent baseline of MAPs were obtained prior to giving the bolus of mivacurium. Decline in MAP due to mivacurium alone could be more accurately obtained with this method. The decline of the MAP due to the dose of mivacurium in the subjects of this study cannot be isolated from those who experienced a decline of MAP due to the induction dose of propofol or the use of volatile inhalation agents.

Conclusions

It can be concluded from this study that there is a shorter time to loss of twitch response at the orbicularis oculi than at the adductor pollicis using 0.2 mg/kg mivacurium chloride in equally divided doses given 30 seconds apart. It can also be concluded that when the loss of twitch response at the orbicularis oculi occurs, the vocal cords are open when using 0.2 mg/kg mivacurium chloride in equally divided doses given 30 seconds apart. Finally, it is concluded that age, sex, weight, and ASA class have no effect on the onset of neuromuscular blockade in the sample population studied.

Clinical Significance

Monitoring the onset of neuromuscular blockade at the orbicularis oculi muscle gives the practitioner a more accurate monitor of laryngeal muscle paralysis than does monitoring the adductor pollicis. This correlation of the orbicularis oculi and laryngeal muscle paralysis allows for rapid placement of the endotracheal tube following laryngeal muscle paralysis. This rapid placement of the endotracheal tube decreases the risk for gastric aspiration and the onset of hypoxia.

Implications for Further Studies

A larger sample population using the same study techniques may explain the slight differences found between male and female subjects and the time required to obtain 100% neuromuscular blockade. A larger sample population may also provide more supportive data correlating changes in MAP and the onset of neuromuscular blockade. A study monitoring the onset and cardiovascular effects of 0.2 mg/kg mivacurium used in split dosages would be beneficial to practitioners. The resulting changes in histamine release and MAP could be measured after maintenance of a stable baseline of MAP had been obtained following the induction of anesthesia. This would allow for a more accurate representation of the effect of dividing the dose of mivacurium.

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