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Is Intramuscular Mivacurium an Alternative to Intramuscular Succinylcholine?

Charles B. Cauldwell, M.D., Ph.D., Marie Lau, B.S.,† Dennis M. Fisher, M.D.‡*

Background: **Mivacurium's rapid onset and short duration of action in children suggests that intramuscular administration might treat laryngospasm and facilitate tracheal intubation without producing prolonged paralysis. Accordingly, the authors measured the neuromuscular effects of intramuscular mivacurium in anesthetized infants and children.**

Methods: **Twenty unpremedicated infants and children (3 months to 5 yr of age) were anesthetized with nitrous oxide and halothane and permitted to breathe spontaneously. When anesthetic conditions were stable, mivacurium was injected into the quadriceps or deltoid muscle. Minute ventilation and adductor pollicis twitch tension were measured. The initial mivacurium dose was 250 μg/kg and was increased (to a maximum of 800 μg/kg, at which dose the trial was ended) or decreased according to the response of the previous patient, the goal being to bracket the dose producing 80–90% twitch depression within 5 min of drug administration.**

Results: **No patient achieved >80% twitch depression within 5 min of mivacurium administration. Peak twitch depression was 90 ± 13% (mean ± SD) for infants and 88 ± 15% for children at 15.0 ± 4.6 min and 18.4 ± 6.4 min, respectively. Ventilatory depression (a 50% decrease in minute ventilation or a 10-mmHg increase in end-tidal carbon dioxide tension) occurred at 9.0 ± 4.4 min in nine infants and 13.6 ± 7.5 min in 10 children; ventilatory depression did not develop in one infant given a dose of 350 μg/kg. Time to peak twitch depression or ventilatory depression was not faster with larger doses.**

Conclusions: **Although ventilatory depression preceded twitch depression, both occurred later with intramuscular mivacurium than would be expected after intravenous mivacurium or intramuscular succinylcholine. The authors speculate that the onset of intramuscular mivacurium is too slow to treat laryngospasm or to facilitate routine tracheal intubation in infants or children, despite administration of large doses. (Key words: Anesthesia: pediatric. Muscle relaxants: mivacurium. Respiratory effects: muscle relaxants.)**

NEUROMUSCULAR blockade often is desired during induction of anesthesia in pediatric patients, either to treat laryngospasm or to facilitate routine tracheal intubation. If venous access has not been obtained, alternate routes to administer muscle relaxants might be desirable or necessary. Administration of succinylcholine, either intramuscularly[1,2] or intralingually,[3] produces paralysis, although of lesser intensity and slower onset than intravenous administration. However, the many adverse effects associated with succinylcholine suggest that it not be used in children.[4]

Mivacurium is a new nondepolarizing muscle relaxant that has a rapid onset in children when administered intravenously.[5,6] We speculated that intramuscular administration might achieve sufficiently rapid onset to permit the use of mivacurium as an alternative to intramuscular succinylcholine for tracheal intubation. However, relative to intravenous administration, absorption of intramuscular mivacurium is likely to be delayed, resulting in lower peak concentrations and lesser effect, and perhaps the need to administer larger doses to achieve adequate paralysis. Although larger intramuscular doses might prolong paralysis, we speculated that mivacurium's duration of action might be clinically acceptable because of its rapid metabolism by plasma cholinesterase.[7]

We evaluated the neuromuscular effects of intramuscular mivacurium. Consistent with other studies of muscle relaxants, we measured neuromuscular block at the adductor pollicis. However, measurements of adductor pollicis twitch depression provide limited information regarding intubating conditions; in contrast, neuromuscular block of the respiratory muscles likely parallels intubating conditions.[8,9] Therefore, in the present study, we use an indirect measure of neuromuscular block of the respiratory muscles, *i.e.*, the effect of mivacurium on spontaneous ventilation.

* Assistant Clinical Professor of Anesthesia. Current position: Department of Anesthesiology, Children's Hospital of Michigan, Detroit.

† Staff Research Associate.

‡ Professor of Anesthesia and Pediatrics.

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Address reprint requests to Dr. Fisher: Department of Anesthesia, University of California, San Francisco, 521 Parnassus Avenue, San Francisco, California 94143-0648.

Methods

After obtaining an Investigational New Drug Exemption from the Food and Drug Administration and approval from our Committee on Human Research, we obtained informed consent from the parents of 20 pediatric patients (ASA physical status 1 (n = 12) or 2 (n = 8)) undergoing a variety of elective surgical procedures. Patients were divided into two groups by age: infants (3–11 months, n = 10) and children (18 months–5 yr, n = 10). Patients were excluded if they or their family had a history of bleeding disorders, neuromuscular disease, or persistent paralysis after anesthesia. No patient received aminoglycoside antibiotics before or during anesthesia.

Patients were not premedicated. Anesthesia was induced by inhalation of nitrous oxide and halothane, and tracheal intubation was accomplished without administration of muscle relaxants. Anesthesia was maintained with 60% N_2O and 0.8–1.0 MAC halothane (end-tidal concentration), adjusted for age[10]; no opioids or other intravenous anesthetics were administered. Patients breathed spontaneously *via* a pediatric circle system (Marquest, Englewood, CO). When anesthetic conditions, twitch tension, and minute ventilation were stable, 2 mg/ml mivacurium was administered as a single injection into the quadriceps (n = 16) or deltoid (n = 4) muscle. The dose of mivacurium for the first patient in each age group was 250 μg/kg. The dose administered to each subsequent patient was based on the peak adductor pollicis response in the previous patient during the first 5 min after injection: If twitch tension decreased >90%, the dose was decreased by 50–100 μg/kg; if twitch tension decreased 80–90%, the dose was not changed; if twitch tension decreased <80%, the dose was increased by 50–100 μg/kg (to a maximum of 800 μg/kg). This "up-down" technique, similar to that used to determine minimum alveolar concentration,[11] was designed to bracket the dose of mivacurium that would depress twitch tension 80–90% during the 5 min after intramuscular administration. If ventilatory depression occurred (defined as spontaneous minute ventilation decreasing 50% from the control value, a 10-mmHg increase in end-tidal carbon dioxide tension, or hemoglobin oxygen saturation <90%), mechanical ventilation was instituted.

Supramaximal square-wave train-of-four stimuli were administered at 2 Hz every 12 s to the ulnar nerve *via* needle electrodes at the wrist. Evoked tension of the adductor pollicis was measured using a Grass FT-03 force transducer (Quincy, MA) while maintaining a preload of 50–100 g. The force signal was amplified (DC Bridge Signal Conditioner, Gould, Valley View, OH), digitized (NB-MIO-16, National Instruments, Austin, TX) on a Macintosh IIci computer, and displayed (LabView, National Instruments). The ratio of the first component of the train-of-four (T1) to its control value was determined. Each train-of-four also was recorded on a strip-chart recorder (TA240, Gould).

Minute ventilation was measured using a calibrated Fleish pneumotachograph (Instrumentation Associates, New York, NY) placed between the breathing circuit and the tracheal tube. The flow signal was amplified (CD15 Carrier Demodulator, Validyne, Northridge, CA), digitized on a Macintosh IIci computer, and the inspiratory signal (corrected for flow to the capnograph) integrated in 12-s epochs (LabView). Respiratory gas was sampled through a catheter placed through the wall of the tracheal tube, and carbon dioxide tension was determined by infrared analysis (Capnomac Ultima, Datex, Helsinki, Finland); peak (end-tidal) values during each 12-s epoch were determined using LabView. Hemoglobin oxygen saturation was measured continuously (N200 Oximeter, Nellcor, Hayward, CA). Blood pressure and heart rate (Dinamap, Critikon, Tampa, FL) were measured at frequent intervals for 30 min after mivacurium administration. The injection site and the skin of the trunk and face were observed after injection until the patient was discharged from the post anesthesia care unit for erythema or other signs consistent with histamine release.

Magnitude of twitch depression at 5 min and peak depression of twitch tension (expressed as a percentage decrease from the control value), as well as times to 10% twitch depression (latency), peak depression (onset), and 90% recovery of twitch tension (duration of action), were determined. Minute ventilation at 1 and 4 min (expressed as a percentage of the control value) and time to ventilatory depression were recorded. Values for infants and children were compared using Student's *t* test for unpaired data; the effect of dose on twitch onset, magnitude of peak effect, and duration of action and time to ventilatory depression was examined using analysis of linear regression. For all statistical comparisons, $P < 0.05$ was considered significant. Values for blood pressure and heart rate were examined for changes exceeding 20% of the control value.

Table 1. Demographic Data and Time Course of Adductor Pollicis Twitch and Ventilatory Depression (Mean ± SD) in Infants and Children Given Intramuscular Mivacurium

	Infants	Children
n	10	10
Age	5.2 ± 2.8 months	2.9 ± 1.4 yr
Weight (kg)	7.1 ± 1.4	14.0 ± 3.2
Dose range (μg/kg)	250–800	250–800
Twitch depression at 5 min (% of control)	13 ± 21	0 ± 2
Time to 10% twitch depression (min)	6.8 ± 3.5	10.4 ± 4.6
Time to peak twitch depression (min)	15.0 ± 4.6	18.4 ± 6.4
Peak twitch depression (% of control)	90 ± 13	88 ± 15
Time to 90% recovery of twitch tension (min)*	46 ± 9	58 ± 18
Ventilation at 1 min (% of control)	148 ± 49	139 ± 30
Ventilation at 4 min (% of control)	90 ± 33	101 ± 15
Time to ventilatory depression (min)†	9.0 ± 4.4‡	13.6 ± 7.5

* Excludes one infant and one child (see results).

† Ventilatory depression was defined as a 50% decrease in minute ventilation, a 10-mmHg increase in end-tidal P_{CO_2}, or Sp_{O_2} <90%.

‡ n = 9 (see results).

Results

No patient developed >80% twitch depression within 5 min; consequently, each patient received a larger dose than the previous patient in the same age group, and the trial was abandoned after the dose of 800 μg/kg. Twitch depression at 5 min was minimal (table 1, fig. 1). Onset time (fig. 2) and magnitude of peak effect (fig. 3) in infants and children and duration of action in children (fig. 4) were not related to dose. For infants, duration of action increased with increasing dose ($P < 0.05$), although the magnitude of the increase was small ($0.03\ \text{min} \cdot \mu\text{g}^{-1} \cdot \text{kg}^{-1}$). Magnitude of peak twitch depression, twitch depression at 5 min, latency, onset time, and duration of action were similar in infants and children. In two patients, duration of action could not be determined: Monitoring was discontinued in one infant given 600 μg/kg mivacurium when twitch tension recovered to 70% of control at 46 min; edrophonium was given to antagonize paralysis in one child given 550 μg/kg when twitch tension was 22% of control at 27 min. In the remaining patients, twitch tension recovered to within 20% of the control value and a train-of-four ratio exceeding 75%.

Minute ventilation typically increased at 1 min after injection of mivacurium, despite no change in surgical stimulation (table 1, fig. 1). Minute ventilation was not depressed at 4 min. All but one patient (an infant given 350 μg/kg) developed ventilatory depression (fig. 5); 16 demonstrated a 50% decrease in minute ventilation; and three children (given doses of 400, 450, and 550 μg/kg, respectively) demonstrated a 10-mmHg increase in carbon dioxide tension. Minute ventilation at 1 and

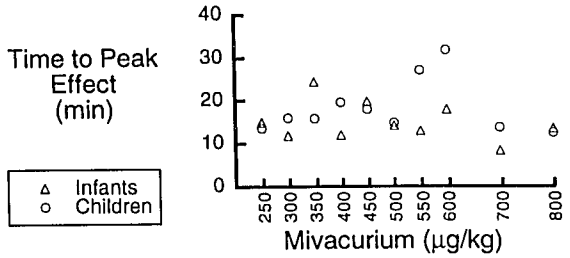

Fig. 2. Onset time (time to peak twitch depression) is displayed as a function of dose for infants (n = 10) and children (n = 10).

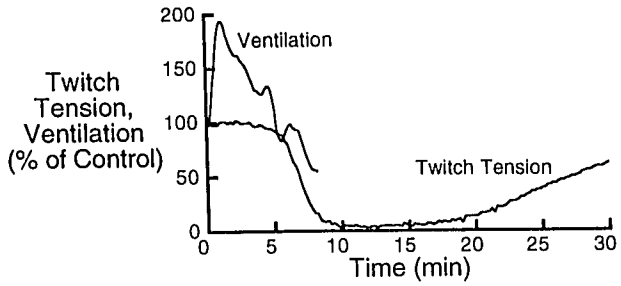

Fig. 1. The time course of twitch depression and ventilation (both normalized to the initial value) is shown for an infant given 400 μg/kg intramuscular mivacurium at time 0. Latency of depression of both twitch and ventilation is large.

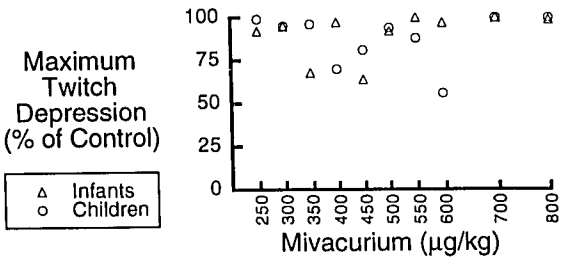

Fig. 3. Magnitude of peak twitch depression is displayed as a function of dose for infants (n = 10) and children (n = 10).

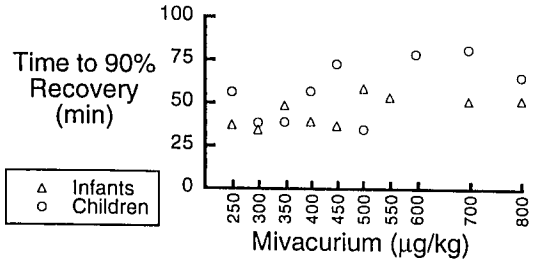

Fig. 4. Duration of action (time to 90% recovery of twitch tension) is displayed as a function of dose for infants and children. For infants, duration of action increased with dose ($P < 0.05$ by analysis of linear regression). Values are not shown for one infant and one child (see results).

4 min and time to ventilatory depression was similar for infants and children. Time to ventilatory depression was not related to dose for either infants or children.

No patient demonstrated a >20% decrease in blood pressure or a >20% change in heart rate within 10 min of intramuscular injection of mivacurium (later increases in heart rate were attributed to surgical stimulation). Five patients developed mild erythema at the injection site, and one developed mild erythema over the chest wall; these resolved spontaneously. There were no other signs of histamine release.

Discussion

Our study originally was designed to determine the dose of intramuscular mivacurium producing 80–90% twitch depression within 5 min of injection, then to assess intubating conditions in patients given twice that dose. However, when onset time did not improve with progressively larger doses and our largest dose (800 μg/kg = 0.4 ml/kg) failed to depress twitch tension of the adductor pollicis to less than 80% of control within 5 min, we terminated our clinical trial. Assuming that tracheal intubation requires profound paralysis, our findings suggest that a single intramuscular injection of mivacurium, even in large doses, is unlikely to facilitate routine tracheal intubation in infants or children. Although our findings suggest that intramuscular mivacurium is also too slow in onset to treat laryngospasm in pediatric patients, perhaps a lesser degree of neuromuscular blockade is adequate in that clinical situation—a recent clinical report suggests that small doses of succinylcholine may be adequate to treat laryngospasm.[12] However, our study design does not permit any conclusions about the dose of mivacurium necessary to treat laryngospasm.

Onset of intramuscular mivacurium was slow compared with the reported time of onset with intravenous administration. For example, Sarner *et al.*[5] and Goudsouzian *et al.*[6] demonstrated that 200–250 μg/kg mivacurium completely depressed twitch tension in <2 min in infants and children anesthetized with nitrous oxide and halothane. The lesser and delayed paralysis with administration *via* nonintravenous routes has been reported with intramuscular[1,2] and intralingual[3] succinylcholine, intramuscular atracurium,[13] and subcutaneous pancuronium[14] and is consistent with delayed absorption resulting in lower peak concentrations in plasma and at the neuromuscular junction. However, despite intramuscular administration delaying succinylcholine's onset, a dose of 4 mg/kg (approximately 9 times the ED_{95}[15]) produces >85% twitch depression at 3.9 ± 0.5 min,[1] far earlier than paralysis with equipotent doses of intramuscular mivacurium (800 μg/kg approximating 8 times the ED_{95}[6]).

Duration of action of intramuscular mivacurium exceeded that seen with intravenous administration of smaller doses (<20 min with 200–250 μg/kg).[5,6] Our longer duration of action likely results from two factors. First, mivacurium probably is absorbed slowly from muscle, as indicated by the delayed peak effect. Second, we administered doses far exceeding those recommended for intravenous administration—the absorption of larger doses is likely to prolong duration of action. Of note, the largest doses we administered did not markedly lengthen duration of action (fig. 4); this finding contrasts with the marked increase in vecuronium's duration of action with large doses[16] and is likely the result of mivacurium's rapid elimination by cholinesterase.[7] Although we did not measure pseudocholinesterase activity, the absence of markedly prolonged recovery in any of our patients suggests that none had abnormal enzymatic activity.

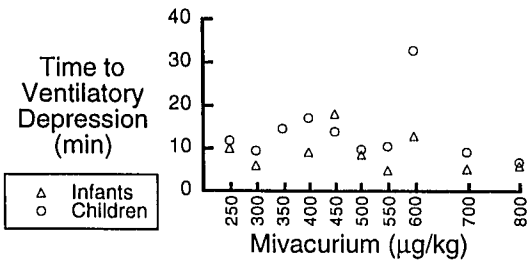

Fig. 5. Time to ventilatory depression is displayed as a function of dose for infants and children. Ventilatory depression did not develop in one infant given 350 μg/kg mivacurium.

With the exception of Mazze and Dunbar's report of the onset of apnea after intralingual succinylcholine,[3] most studies examining the onset of muscle relaxants in children have measured only the evoked response of the adductor pollicis. However, tracheal intubation and treatment of laryngospasm require paralysis of the airway muscles rather than of the adductor pollicis. Donati *et al.*[8,9] demonstrated that vecuronium depresses the airway muscles before the adductor pollicis; similar findings would be expected for mivacurium. Thus, we expected that, even if intramuscular mivacurium had a slow onset at the adductor pollicis, onset at the respiratory muscles might be sufficiently rapid to be clinically useful. Optimally, we might have measured the evoked tension of the vocal cords and the electromyogram of the diaphragm as has been performed in adults[17,18]; however, these techniques require placing a cuffed tracheal tube and have not been verified in children. Alternatively, we might have induced laryngospasm in spontaneously breathing children, and then administered mivacurium intramuscularly and measured the time to improved chest excursion or breath sounds. Ethical considerations prevented these alternate study designs, necessitating an indirect measure of the onset of ventilatory depression. Our study design permitted us to determine that ventilatory depression typically preceded twitch depression. This finding was expected based on previous studies of muscle relaxants. However, even with very large doses, ventilatory depression was minimal within 4 min of mivacurium injection. Although intubating conditions may have improved before the observed onset of ventilatory depression, we speculate that the onset of intramuscular mivacurium is too slow to be of practical value in pediatric anesthesia. We also observed increased minute ventilation 1 min after mivacurium administration, despite no change in surgical stimulus; we attributed this increase to pain from the intramuscular injection.

Despite administration of doses of mivacurium larger than typically recommended for administration to children, we observed neither hypotension nor other signs of significant histamine release. The slow absorption of mivacurium most likely limited the peak plasma concentration, just as slow administration of mivacurium minimizes its cardiovascular effects compared with bolus administration.[19]

Two other considerations limit the usefulness of intramuscular mivacurium in pediatric patients. First, if large doses intended for intramuscular administration were inadvertently absorbed intravenously, high plasma concentrations might produce profound hypotension or other signs of histamine release.[19] Second, if large doses were administered to a cholinesterase-deficient patient, continued absorption of mivacurium might markedly prolong paralysis.[20,21] These considerations resulted in our limiting the maximum dose to 800 μg/kg; however, larger doses might be effective (although possibly associated with more frequent adverse effects).

In summary, time to peak adductor pollicis depression after large doses of intramuscular mivacurium consistently exceeded 10 min. Although ventilatory depression typically preceded twitch depression, a latency exceeding 4 min limits the usefulness of intramuscular mivacurium for pediatric anesthesia.

References

1. Liu LMP, DeCook TH, Goudsouzian NG, Ryan JF, Liu PL: Dose response to intramuscular succinylcholine in children. ANESTHESIOLOGY 55:599–602, 1981

2. Sutherland GA, Bevan JC, Bevan DR: Neuromuscular blockade in infants following intramuscular succinylcholine in two or five per cent concentration. Can Anaesth Soc J 30:342–346, 1983

3. Mazze RI, Dunbar RW: Intralingual succinylcholine administration in children: An alternative to intravenous and intramuscular routes? Anesth Analg 47:605–615, 1968

4. Rosenberg H, Gronert GA: Intractable cardiac arrest in children given succinylcholine (letter). ANESTHESIOLOGY 77:1054, 1992

5. Sarner JB, Brandom BW, Woelfel SK, Dong M-L, Horn MC, Cook DR, McNulty BF, Foster VJ: Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia. Anesth Analg 68:116–121, 1989

6. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miler V, McNulty BF, Savarese JJ: Neuromuscular and cardiovascular effects of mivacurium in children. ANESTHESIOLOGY 70:237–242, 1989

7. Cook DR, Stiller RL, Weakly JN, Chakravorti S, Brandom BW, Welch RM: In vitro metabolism of mivacurium chloride (BW B1090U) and succinylcholine. Anesth Analg 68:452–456, 1989

8. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the diaphragm, the orbicularis oculi, and adductor pollicis muscles. ANESTHESIOLOGY 73:870–875, 1990

9. Donati F, Meistelman C, Plaud B: Vecuronium neuromuscular blockade at the adductor muscles of the larynx and adductor pollicis. ANESTHESIOLOGY 74:833–837, 1991

10. Gregory GA, Eger EI, Munson ES: The relationship between age and halothane requirement in humans. ANESTHESIOLOGY 30:488–491, 1969

11. Dixon WJ: Quantal-response variable experimentation: The up-and-down method, Statistics in Endocrinology, Proceedings. Edited by McArthur JW, Colton T. Cambridge, MIT, 1967, pp 251–267

12. Chung DC, Rowbottom SJ: A very small dose of suxamethonium relieves laryngospasm. Anaesthesia 48:229–230, 1993

13. Johr M, Can U: Pediatric anesthesia without vascular access: Intramuscular administration of atracurium (letter). Anesth Analg 76:1162–1163, 1993

14. Iwasaki H, Namiki A, Omote T, Omote K: Neuromuscular effects of subcutaneous administration of pancuronium. ANESTHESIOLOGY 76:1049–1051, 1992

15. Meakin G, McKiernan EP, Morris P, Baker RD: Dose-response curves for suxamethonium in neonates, infants and children. Br J Anaesth 62:655–658, 1989

16. Sloan MH, Lerman J, Bissonnette B: Pharmacodynamics of high-dose vecuronium in children during balanced anesthesia. ANESTHESIOLOGY 74:656–659, 1991

17. Donati F, Plaud B, Meistelman C: A method to measure elicited contraction of laryngeal adductor muscles during anesthesia. ANESTHESIOLOGY 74:827–832, 1991

18. Donati F, Antzaka C, Bevan D: Potency of pancuronium at the diaphragm and the adductor pollicis muscle in humans. ANESTHESIOLOGY 65:1–5, 1986

19. Savarese JJ, Ali HH, Basta SJ, Scott RP, Embree PB, Wastila WB, Abou Donia M, Gelb C: The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. ANESTHESIOLOGY 70:386–394, 1989

20. Ostergaard D, Jensen FS, Jensen E, Skovgaard LT, Viby-Mogensen J: Influence of plasma cholinesterase activity on recovery from mivacurium-induced neuromuscular blockade in phenotypically normal patients. Acta Anaesthesiol Scand 36:702–706, 1992

21. Maddineni VR, Mirakhur RK: Prolonged neuromuscular block following mivacurium. ANESTHESIOLOGY 78:1181–1184, 1993