EFFECT OF AGE ON MIVACURIUM PHARMACODYNAMIC PARAMETERS USING MECHANOMYOGRAPHY NEUROMUSCULAR MONITORING

Ashraf A. Dahaba' MD, MSc, PhD
Department of Anaesthesiology and Intensive Care Medicine
Graz Medical University, Graz, Austria.

ABSTRACT

Currently mivacurium chloride is the only non-depolarizing neuromuscular blocking drug with a short duration of action. The aim of the study was to compare mivacurium infusion requirements in elderly and young patients.

Twenty young patients (18-40 years) and 20 elderly patients (65-79 years) undergoing elective surgical procedures were included in the study. Neuromuscular block at the adductor pollicis muscle was evaluated using the Relaxometer mechanomyograph (Groningen University Holland). An initial bolus of mivacurium 0.15 mg/kg was administered over 30 s. Thereafter, infusion rates of 0.5 mg kg' W' were started after T_1 (first twitch of the TOE train of four) 25% recovery. Neuromuscular block was maintained at t 25% by 3-mm-intervals ±0.05mg kg' WI (±10% of the initial rate) infusion rate adjustments.

Intubating conditions were excellent to good in 90-100% of the young and elderly patients, with adequate hemodynamic stability. Fifteen mm from the start of infusion, rate requirements initially increased in the young group after that it decreased to 92.9% +13.5 towards the end of the 30-mm. Whereas rate requirements in the elderly group decreased from the beginning to 78.5% +13.6 towards the end of the 30-mm. Beyond the first 30-mm, mean infusion requirement in the young group was significantly higher than the infusion requirement in the elderly group.

In conclusion mivacurrum 0.15 mg/kg yielded favorable intubating conditions with adequate hemodynamic stability in both young and elderly patients. Elderly patients required significantly lower infusion rates than young patients.

INTRODUCTION

Although rocuronium bromide and cisatracurium are currently the mast widely used neuromuscular blocking drugs (NMBD), mivacurium chloride is stilt the only non-depolarizing NMBD with a short duration of action. This makes it particularly useful for brief surgical procedures. Mivacurium is classified as "short acting" because it has duration of action that is approximately one-half that of the inter-mediate agent rocuronium and approxi-mately twice that of the ultra-short acting suxamethonium[(1)]. Mivacurium is non-cumulative and easily adjustable when administered as continuous infusion[(2)].

Hydrolysis by plasma butyryl-cholinesterase (pseudocholinesterase) but not acetyl-chotinesterase (true cholinesterase) is the primary mute for mivacurium excretion. Mivacurium hydrolysis yields a quaternary monoester, a quatemary alcohol and a dicarboxylic acid. A small amount of mivacuriuni is excreted unchanged in urine and bile, however urine and bile are important elimination routs for its main metabolites[(2)]. The effective $dose_{95}$ (ED_{95}) for mivacurium chloride during stable narcotic anesthesia is 0.07 mg/kg (range 0.06 -0.09 mg/kg)[(1)].

The aim of the study was to compare mivacurium chloride infi.ision requirements and intubation conditions in elderly and young patients.

PATIENTS AND METHODS

A prospective controlled clinical consecutive study was conducted in conformity with the guidelines of "Good clinical research practice (GCRP) in pharmacodynamic studies of neuro-muscular blocking agents"[(3)], and the "Consolidated standards of reporting trials (CONSORT)-statement"[(4)].

Forty consecutive, ASA I-III patients, undergoing elective surgical procedures expected to last between 30 min-2 h were included in the study; 20 young patients between 18-40 years and 20 elderly patients between 65-79 years.

After Graz Medical University ethics committee approval, all patients who

agreed to participate in the study gave a written informed consent. Potential participants with history of neurological, neuromuscular disorders, clinically significant hepatic, renal disease, small joint arthritis, with body mass index <20-24>[5], or patients on treatment with drugs thought to interfere with neuromuscular transmission, were excluded from the study.

Oral midazolam 7.5 mg was the only premedication given 1 h before surgery. One arm was positioned comfortably on an arm board and restrained from movement by straps. The area above the ulnar nerve at the wrist, where the electrodes are to be placed was cleaned to ensure adequate contact. The neuromuscular block at the adductor pollicis muscle was evaluated using the Relaxometer mechanomyograph (Oroningen University Holland)[6]. The force transducer was attached to the thumb and the ulnar nerve was stimulated supramaximally at the wrist (pulse width 200 Its, square wave) via surface electrodes with train-of-four (TOE) stimuli (2 Hz for 2 s) at 12 s interval.

The preload on the thumb was maintained between 200-400 g throughout the whole procedure. The mechanomyograph was connected to a laptop computer via the serial port. Data were continuously collected and recorded using the "AZG-Relaxometer 5.0" program until all patients filly recovered from neuromuscular block. T_1 (first twitch of the TOE) expressed as percentage of control response and the TOF ratio (T4: T_1) were used for the evaluation of neuromuscular block. Discarding all measurements that changed by 15% than the previous readings filtered artifact readings. Core temperature was monitored using an esophageal probe, whereas palmar skin temperature at the thenar area was monitored by the temperature probe of the mechanomyograph. Patients were warmed using a forced-hot-air-blanket (Bair Hugger™ Augustine Medical) to maintain core temperature above 36^0C and skin temperature above 32°C.

Anesthesia was induced with fentanyl 1.5 µg/kg and propofol 2-3 mg/kg until the eyelash reflex was lost, during which patients were ventilated via a facemask. After T_1% baseline stabilization, defined as a T_1% response with variation of less than ±2% for the last 3 min, mivacurium 0.15 mg/kg (2 x ED_{95}) was administered over 30 s. Tracheal intubation was attempted when T, was maximally suppressed.

The lungs were mechanically ventilated with 40% oxygen in air. Anesthesia was maintained with propofol 6-9 mg kg' h' and remifentanil 0.1-0.3 µmg kg^{-1} min infusions. Ventilation was adjusted to maintain an end-tidal carbon dioxide ($Etco_2$) in the range of 25-35 mmHg and peripheral oxygen saturation (Spo_2) above 95%. Hemodynamic variables: heart rate (HR), systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) were recorded non invasively every 3 mm. Adverse events, including erythema, post operative nausea and vomiting (PONy) were recorded by the anesthesiologist, anesthesia nurses and post anesthesia care unit (PACU) nurses.

The following pharmacodynamic parameters were calculated:

Onset time: time from mivacurium administration until 0% T_1 response or maximum T, suppression.

Dur_{25}: time from mivacurium administration until 25% T_1 recovery.

Dur_{25-75}: time of T_1 recovery from 25% to 75%.

$Dur_{25-0.8}$: time from 25% T_1 until 0.8 TOF ratio recovery.

Intubating conditions were graded as: excellent (no resistance to laryngoscopy, no movement of vocal cords, limbs or coughing), good (slight resistance to laryngoscopy, movement of vocal cords, limbs or diaphragm), poor (active resistance of the patient to laryngoscopy, closing of vocal cords, vigorous mavement of die limbs or coughing)[7].

Mivacurium infusion was started at an initial rate of 0.5 mg kg' If' after T_1recovered to 25%. Neuromuscular block was thereafter maintained at T, 25% by 3-ruin interval rate adjustments (±0.05 mg kg' Ii', 10% of initial infusion rate). The 3-mm rate adjustments were continuously recorded. Data were expressed as a percentage of mivacurium initial infusion rate of 0.5 mg kg Twenty minutes before the expected end of the operation mivacurium infusion was stopped and patients were allowed to recover spontaneously up till 0.8 TOE ratio recovery.

Statistical Analysis

Our a-priori power analysis for two-sided t-test showed that a group size of 20 patients would be required to reveal a statistically significant difference between the 2 groups with >80% power (a =0.05). Student (-test was used for the analysis of the differences between the 2 groups. Paired f-test was used fir variables comparisons over time. Intubation conditions were analyzed using Mann-Whitney U-test. The incidence of complications was analyzed using CM-Square test. Data were expressed as mean ±SD. P value of <0.05 was considered statistically significant.

RESULTS

The two groups were comparable with respect to weight, gender, duration of surgery. Elderly patients required significantly less propofol and remifentanil (table 1).

With regards to intubating conditions there were no significant differences between the 2 groups, as mivacurium onset time of 2.4+0.5 mm yielded excellent intubating conditions in 6/20, good in 12/20 and poor in 2/20 young patients. Whereas mivacurium onset time of 1.9±0.4 mm in the elderly patients yielded excellent intubating conditions in 8/20, good in 12/20 and no poor intubating conditions.

In bath groups, following mivacurium initial dose administration there was no change in lift, whereas SAP and DAP declined. There was an increase in SAP, DAP and HR following intubation with no significant differences between the two groups (figure 1). After that the hemodynamic variables did not significantly change aver time.

The infusion rate requirements for the 2 groups changed significantly over the first 30-mm as, 15 mm from the start, the infusion rate increased in the young group to after that it decreased to 92.9% +13.5 towards the end of the 30-mm. Whereas the infusion rate in the elderly group decreased from the beginning to 78.5% f 13.6 towards the end of the 30-mm. The differences between the 2 groups were statistically significant. Beyond the first 30-mm, operations lasted up to 2-h. The mean infusion requirement for the whole 2-h period, in the young group was significantly higher than the infusion requirement in the elderly group. In both groups, the infusions decline over time was along the same course (figure 2).

Initial Dur_{25} as well as Dur_{25-75}, and Dur_{25-80}.pharmacodynamic parameters following the termination of mivacurium infusion were significantly longer in the elderly group compared to the young group (table 2).

Four/20 elderly patients manifested erythema following mivacurium administ-ration compared to 2/20 young patients. None of the patients in our study experienced PONV or other adverse events that could be related to the NMBD.

DISCUSSION

Intubating conditions were excellent to good in 90% of the young patients and after 2min. This is in contrast to a study by Maddineni et al.[8], who reported that mivacurium 0.15 mg/kg did not provide favorable intubating conditions at 2.5 min.

In our study infusion requirements in young patients increased by 11% to 0.55 mg kg^{-1} h^{-1} in the first IS min of infusion, then the rate gradually decreased.

Table (1): Demographic data, anesthetics requirements and duration of surgery.

	Young-group (n=20)	Elderly-group (n=20)	P value
Male/ female	10/10	8/12	0.1126
Weight (kg)	172±7	166±6	0.2667
Remifentanil infusion (µg kg^{-1} min^{-1}	0.18±0.07	0.13±0.05	0.0483
Propofol infusion (mg kg^{-1} h^{-1})	8.3±1.5	5.4±0.8	0.0364
Duration of surgery (min)	109.9±37.3	124.9±33.1	0.4431

Means ±SD

Table (2): Mivacurium Pharmacodynamic parameters.

	Young-group (n=20)	Elderly-group (n=20)	P value
Dur25	19.9±4.4	24.8±5.5	0.0277
Dur25-75	12.0±6.6	16.5±7.8	0.0455
Dur25-0.8	15.9±4.8	19.4±12.6	0.0384

Mean (min)±SD, Dur25: time from mivacurium administration till 25% T1 recovery. Dur25-75: time of T1 recovery from 25% to 75%. Dur25-0.8: time from 25% T1 until 0.8 TOF ratio recovery.
Means ±SD

In the elderly patients infusion requirement increased by 20% to 0.4 mg kg^{-1} h^{-1} in the first 20 min of infusion, after which the rate further declined. The difference over the first 30 min was statistically significant. A lower plasma cholun-esterase concentrations in elderly patients cannot be the only factor causing this difference in mivacurium infusion requirements between the young and elderly patients[9], as in the first 30-min of infusion the rates ran along completely different time courses, whereas plasma cholin-esterase concentrations would not change over time. The difference in infusion requirements between young and elderly patients could be attributed to the fact that mivacurium was distributed to a significantly smaller volume of distribution in elderly patients compared to young patients[10].

Beyond the first 30-min, in both groups, infusion requirements significantly declined over time. The decrease in requirements of both groups was along the same course. Although a study by Basta et al. showed that the pharmacokinetics of a constant mivacurium infusion remains steady over time[10], still in our study compared to the initial infusion rate, infusion requirement after 2-h were 50% lower (0.2 mg kg^{-1} h^{-1}) in young patients and 40% lower (0.25 mg kg^{-1} h^{-1}) in elderly patients, clearly indicating an obvious cumulative effect.

Two studies demonstrated a significant decline in mean arterial pressure following rapid administration of 0.2 mg/kg mivacurium over 2-3s[11], or over 10-15 s[12]. However when mivacurium was administered over 30 s the authors reported no significant decline from baseline[11,12]. This is in contrast to our results, whereby mivacurium administration over 30 s was still associated with a significant decline in SAP and flAP. This decline lasted only until tracheal intubation and thus required no intervention.

The incidence of erythema experienced by our study patients following mivacurium administration was relatively high, and was higher than previous reports using 0.2 mg/kg[13].

In conclusion mivacurium 0.15 mg/kg yielded favorable intubating conditions with adequate hemodynamic stability in bath young and elderly patients. Elderly patients required significantly lower infusion rates than young patients.

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