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Mild Intraoperative Hypothermia Increases Duration of Action and Spontaneous Recovery of Vecuronium Blockade during Nitrous Oxide–Isoflurane Anesthesia in Humans

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We compared the duration of action and recovery times for vecuronium in normothermic and mildly hypothermic patients. Ten patients were actively cooled to a central body temperature near 34.5° C, and ten were maintained at a normothermic central temperature (>36.5° C); temperature was measured in the distal esophagus. Vecuronium 0.1 mg/kg was administered as an intravenous (iv) bolus to all patients, and the evoked mechanical response to train-of-four stimulation was recorded. Five hypothermic and five normothermic patients were allowed to recover spontaneously. In the remaining five in each group, neostigmine (40 μg/kg) and atropine (20 μg/kg) was administered when the first twitch (T1) height spontaneously recovered to 10% of control (T1 = 10% of the prevecuronium twitch tension). Vecuronium's duration of action (from injection of drug until T1 = 10%) was 28 ± 4 and 62 ± 8 min during normothermia and hypothermia, respectively ($P < 0.05$). The corresponding values for spontaneous recovery from T1 = 10% to TOF ratio >75% were 37 ± 15 and 80 ± 24 min ($P < 0.05$), and for neostigmine-induced recovery were 10 ± 3 and 16 ± 11 min (difference not significant). We conclude that mild hypothermia increases the duration of action of and time for spontaneous recovery from vecuronium-induced neuromuscular blockade. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: fentanyl. Anesthetics, volatile: isoflurane. Muscle: force of contraction. Muscle relaxants: vecuronium. Neuromuscular transmission: adductor pollicis; twitch response. Temperature: central, skin.)

DECREASES in central body temperature significantly influence neuromuscular function, both in the presence and absence of neuromuscular blocking agents.[1–3] Deep hypothermia (28–30° C) during cardiopulmonary bypass is associated with an increased intensity of vecuronium-induced neuromuscular blockade.[2,3] However, the influence of mild intraoperative hypothermia on the action of neuromuscular blocking drugs is not known. Mild central hypothermia occurs commonly during anesthesia, especially in conjunction with cool operating rooms and surgery involving body cavities,[4–6] Because of this we believe it is important to determine the effect, if any, of such mild hypothermia on the duration of action of neuromuscular blocking drugs, in particular the commonly used drug vecuronium. We have previously demonstrated that in the absence of neuromuscular blocking drugs, mild central hypothermia is associated with a decrease in the force of contraction of the adductor pollicis muscle of 10–15% per degree Celsius reduction in muscle temperature.[1] Therefore, we predict that mild central hypothermia prolongs the duration of vecuronium-induced neuromuscular blockade. To test this hypothesis we compared the duration of action and recovery time of vecuronium-induced neuromuscular blockade in normothermic and mildly hypothermic patients undergoing noncardiac surgery during nitrous oxide–isoflurane anesthesia.

Materials and Methods

With approval from our Committee on Human Research and patients' written informed consent, we studied 20 unpremedicated patients of ASA physical status 1 or 2 undergoing elective surgery not involving the abdominal or thoracic cavities. No patients had any disease or were taking any medication that might alter their response to neuromuscular blocking drugs. Anesthesia was induced using thiopental (2–5 mg/kg intravenously [iv]) and inhalation of isoflurane (4–5%), and each patient's trachea was intubated without the use of neuromuscular blocking drugs. Anesthesia was maintained with nitrous oxide (65%) and isoflurane (0.9–1.1% end-tidal concentration), as measured by mass spectrometry. Ventilation was controlled to maintain end-tidal carbon dioxide tension ($P_{E_{CO_2}}$) between 30 and 35 mmHg.

A Grass S88 nerve stimulator delivered supramaximal, square-wave impulses of 0.2-ms duration in a train-of-four (TOF) sequence (2 Hz) *via* 27-G needle electrodes placed adjacent to the ulnar nerve at the wrist. TOF stimuli (2 Hz) were repeated at intervals of 15 s, and the evoked mechanical response of the adductor pollicis muscle was quantitated by a force-displacement transducer (Gould

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Statham UTC3) and displayed on a polygraph. We measured the amplitude of the first response in each train (T1) and the ratio of the amplitude of the fourth response to that of the first (TOF ratio). Control T1 was the response immediately preceding the administration of vecuronium.

Central body temperature was measured by a thermocouple placed in the distal esophagus (Mon-a-therm,® St. Louis, MO). To detect peripheral vasoconstriction, lower arm and fingertip skin-surface temperatures were measured using 1-cm-diameter, self-sticking Mon-a-therm® thermocouple probes.[7]

Patients were divided into four groups of five patients each. Groups 1 and 2 were kept normothermic (central body temperature 36.5–37° C) using a Bair Hugger® forced-air warmer[8] (Augustine Medical, Minneapolis, MN), active airway humidification, low fresh gas flows, and warmed iv fluids. Patients in groups 3 and 4 were actively cooled to a central body temperature of 34–34.5° C by placing circulating water blankets maintained at 5–10° C above and beneath them and by maintaining room temperature below 20° C.

When the central body temperature had stabilized at the desired level (±0.5° C), vecuronium 0.1 mg/kg was administered iv. In the normothermic patients, vecuronium was administered 30–45 min after induction of anesthesia. In the hypothermic patients, because of the time taken for the cooling process, the vecuronium was administered 45–60 min after the induction of anesthesia. Central and skin-surface temperatures and adductor pollicis twitch tension were recorded continuously, and T1 twitch tension at the time of vecuronium administration was used as the control T1 response. Times from the injection of vecuronium until ablation of T1 (onset) and until spontaneous recovery of T1 twitch tension to 10% (duration of action) were measured in all patients. In groups 1 and 3, times from injection of vecuronium until T1 recovered spontaneously to 25 and 75% of control and until the TOF ratio reached 75% were recorded. In groups 2 and 4, when T1 twitch tension recovered to 10%, neostigmine 40 μg/kg and atropine 20 μg/kg were administered, and subsequent recovery times to T1 = 25 and 75% and TOF ratio = 75% were recorded.

The onset and duration of action and recovery times in the normothermic and hypothermic groups were compared using the Mann-Whitney U-test. Differences were considered significant when $P < 0.05$.

Results

The demographic characteristics of all groups were similar (table 1). In the normothermic patients, vecuronium was administered 30–45 min after the induction of anesthesia. Because of the time involved in cooling patients to a central body temperature ~ 34.5° C (groups 3 and 4), vecuronium was administered 45–60 min after induction of anesthesia in these patients. Peripheral vasoconstriction, as defined by a lower arm − fingertip skin temperature gradient of >4°C, did not occur in any patient.[7]

The mean central body temperatures at which vecuronium was administered were 36.5 ± 0.1° C (range 36.4–36.7° C) and 34.7 ± 0.3° C (range 34.3–35.0° C) in normothermic and hypothermic patients, respectively (table 1). In hypothermic patients, central body temperature decreased 0.3 ± 0.2° C during the period after vecuronium administration. The temperature then increased, and during the recovery phase it was within 0.5° C of the temperature at the time vecuronium was administered (table 1).

All patients achieved complete paralysis after vecuronium injection, and the time to achieve this (onset) was not different in the normothermic (122 ± 18 s [mean ± standard deviation (SD)] and hypothermic patients, 135 ± 24 s. In normothermic *versus* hypothermic patients, durations of action (injection to T1 = 10%), 28 ± 4 *versus* 62 ± 8 min respectively, were significantly different (table 2 and fig. 1).

For spontaneous recovery in normothermic *versus* hypothermic patients, the following all were significantly different ($P < 0.05$): recovery index (T1 = 25% to T1

TABLE 1. Group Demographics and Central Body Temperatures

	Normothermia		Hypothermia	
	Spontaneous	Neostigmine-induced	Spontaneous	Neostigmine-induced
Male/female	4/1	2/3	3/2	3/2
Weight (kg)	67 ± 11	63 ± 8	74 ± 15	74 ± 19
Age (yr)	35 ± 14	37 ± 9	33 ± 7	35 ± 13
Central temperature				
When vecuronium injected (° C)	36.5 ± 0.1	36.5 ± 0.1	34.8 ± 0.2	34.7 ± 0.2
When T1 response = 10% (° C)	36.4 ± 0.1	36.4 ± 0.1	34.4 ± 0.4	34.4 ± 0.4
When TOF ratio = 75% (° C)	36.6 ± 0.1	36.5 ± 0.1	34.6 ± 0.4	34.6 ± 0.3

All results are mean ± SD.
Normothermia/hypothermia refers to temperature group; spontaneous/neostigmine-induced refers to neuromuscular recovery.

TABLE 2. Onset and Duration of Action after Vecuronium 0.1 mg/kg in Normothermic and Hypothermic Patients

	Normothermic (n = 10)	Hypothermic (n = 10)
Onset (s) (ablation of T1 response)	122 ± 18 (90–150)	135 ± 24 (105–180)
Duration (min) (injection to T1 = 10%)	28 ± 4 (24–36)	62 ± 8* (45–74)

Mean ± SD; range in parentheses.
* Significantly different from normothermic group ($P < 0.05$).

= 75%), 16 ± 5 *versus* 54 ± 19 min; recovery time (for T1 = 10% to T1 = 75%), 21 ± 6 *versus* 67 ± 10 min; and recovery time (for T1 = 10% to TOF ratio = 75%), 37 ± 15 *versus* 80 ± 54 min (table 3, fig. 2). The times during normothermia were the lesser in every case. In two hypothermic patients in the spontaneous recovery group, the T1 responses had returned to only 83 and 75% and the TOF ratios to only 60 and 45% by the end of surgery; therefore, recovery times in the hypothermic group are underestimated. In both of these patients, neostigmine was administered, and they recovered completely (TOF ratio > 75%) within 10 min).

After the administration of neostigmine 40 μg/kg at T1 = 10%, no significant difference was found between normothermic and hypothermic patients with respect to recovery index (T1 from 25 to 75%), 2.4 ± 0.9 *versus* 2.8 ± 1.1 min, respectively; recovery to T1 = 75%, 3.9 ± 1.8 *versus* 5.2 ± 1.6 min, respectively; and TOF ratio = 75%, 10 ± 3 min *versus* 16 ± 11 min, respectively (table 3, fig. 3).

Discussion

The influence of temperature on the neuromuscular blocking action of nondepolarizing neuromuscular blocking drugs is controversial. In previous *in vitro* or *in vivo* animal studies, hypothermia either increased[9–11] or decreased[12–15] the effect of *d*-tubocurarine. A reduction in temperature to 34° C either increased[16] or had no effect on pancuronium-induced neuromuscular blockade.[17] This variability in results may be attributable to the use of different experimental techniques, varying degrees of hypothermia, species variation, and differences in the dose of drug. In a previous investigation in humans during nitrous oxide–opioid anesthesia, the intensity of *d*-tubocurarine-induced blockade decreased during local cooling conditions.[18] However, very small doses of *d*-tubocurarine were administered, and the expected enhancement of *d*-tubocurarine's effect at low temperatures may have been overwhelmed by an increase in acetylcholine release due to temperature reduction.[19]

The purpose of the current study was primarily to determine whether or not intraoperative hypothermia, of a degree that is likely to occur during normal anesthesia,[4–6] influenced the time course of vecuronium-induced neuromuscular blockade. We did not set out to study pharmacodynamic or pharmacokinetic mechanisms because we did not know at the outset if mild hypothermia would have any significant effect on the time course of action of vecuronium. We cannot, therefore, address the possible mechanisms underlying the effects we observed. Ham *et al.* studied the pharmacodynamics and pharmacokinetics of *d*-tubocurarine during a greater degree of hypothermia (mean central temperature 31.9 °C) than we used.[20] Although they found an increased recovery index during hypothermia, they did not conclusively demonstrate any significant pharmacodynamic or pharmacokinetic difference between their hypothermic and normothermic patients. Further study is required to determine the mechanisms underlying the effects we observed.

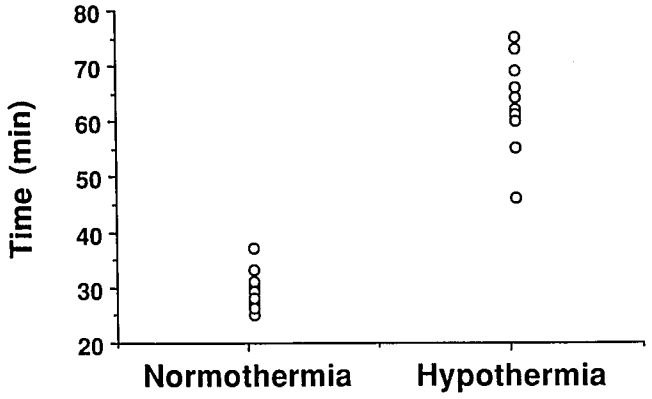

FIG. 1. Durations of action of vecuronium in ten normothermic (36.4 ± 0.1° C) and ten mildly hypothermic (34.4 ± 0.4° C) patients. Duration of action was significantly prolonged during hypothermia (62 ± 8 min compared to 28 ± 4 min at normothermia; mean ± SD).

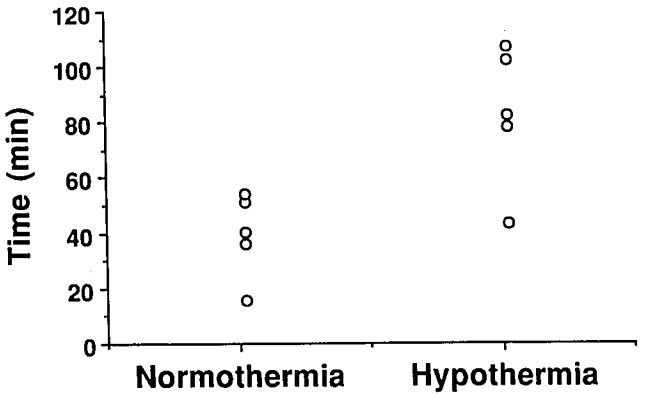

FIG. 2. Spontaneous recovery times of vecuronium, from T1 = 10% until TOF ratio = 75%, in five normothermic (36.6 ± 0.1° C) and five mildly hypothermic (34.6 ± 0.3° C) patients. Spontaneous recovery was significantly prolonged during hypothermia (80 ± 24 min compared to 37 ± 15 min during normothermia; mean ± SD). Two hypothermic patients recovered only to TOF ratios of 45 and 60% (recovery times 80 and 76 min, respectively).

TABLE 3. Spontaneous and Neostigmine-induced Recovery of Neuromuscular Function

	Normothermic Spontaneous (n = 5)	Hypothermic Spontaneous (n = 5	Normothermic Neostigmine-induced (n = 5)	Hypothermic Neostigmine-induced (n = 5)
Recovery index (min) (T1 = 25% to 75%)	16 ± 5 (8–20)	54 ± 19* (24–74)	2.4 ± 0.9 (2.0–4.0)	2.8 ± 1.1 (2.0–4.0)
Recovery time (min) for (T1 = 10% to 75%)	21 ± 6 (11–25)	67 ± 10* (31–90)	3.9 ± 1. (3–7)	5.2 ± 1.6 (4–7)
Recovery time (min) for (T1 = 10% to TOF ratio= 75%)	37 ± 15 (13–52)	80 ± 24*† (41–105)	10.0 ± 3.0 (7–14)	16.0 ± 11.0 (7–35)

Mean ± SD; range in parentheses.
* Significantly different from normothermic group ($P < 0.05$).
† One patient recovered only to TOF = 45% and one to TOF ratio = 60% before the end of surgery.

The intensity of vecuronium-induced neuromuscular blockade increases during cardiopulmonary bypass.[2,3] However, these results cannot be applied to the more normal situation of mild hypothermia. First, these patients generally are much cooler than those undergoing noncardiac surgery. Second, during cardiopulmonary bypass, liver and kidney blood flow may be significantly reduced, such that the metabolism of vecuronium is decreased.[21,22] Third, plasma protein binding capacity decreases during cardiopulmonary bypass, thereby increasing the free fraction of the neuromuscular blocking drug in plasma and the intensity of blockade for a given dose of drug.[23,24]

Because of the time involved in the cooling process, there was a small difference in the duration of exposure to isoflurane before the administration of vecuronium in the normothermic and hypothermic patients. The degree to which this difference in duration of exposure may have influenced our results must be considered. Stanski *et al.* demonstrated a small time-dependent increase in sensitivity, 9% per hour, to *d*-tubocurarine during enflurane anesthesia.[25] Eriksson *et al.* found that the duration of neuromuscular blockade following a small bolus of vecuronium was 21 min before and 24 min after a 90-min exposure to isoflurane, 0.5%.[26] This represents an increase in duration of only 14%. These two studies show that the duration of anesthetic exposure has only a small effect on neuromuscular blockade. Therefore, we believe that the small difference in anesthetic exposure between the normothermic and hypothermic patients made only a minimal, if any, contribution to the increase in the duration of neuromuscular blockade in the hypothermic patients.

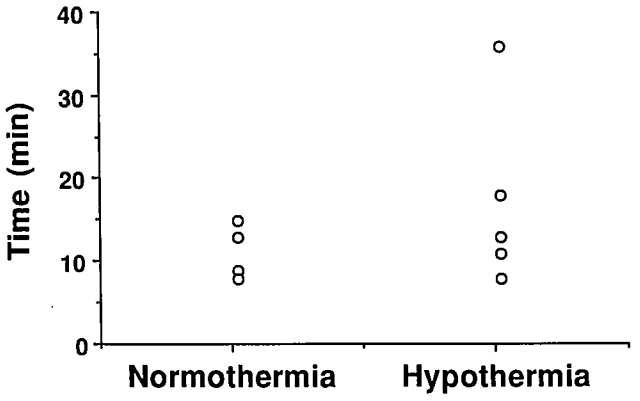

FIG. 3. Neostigmine-induced recovery times of vecuronium, from T1 = 10% until TOF ratio = 75%, in five normothermic (36.5 ± 0.1° C) and five mildly hypothermic (34.6 ± 0.4° C) patients. Only four hypothermic data points are seen because the times were identical in two patients. No statistically significant difference was found between normothermic and hypothermic patients (10 ± 3 min and 16 ± 11 min, respectively; mean ± SD).

We observed not only an increased duration of action of vecuronium during mild hypothermia but also a decreased rate of recovery. In particular, our mean value for the time from T1 = 10% to TOF ratio = 75% is likely to be an low estimation of the true value. This is because in two patients TOF ratio had recovered to only 45 and 60% at the end of surgery.

In the clinical situation, patients seldom are hypothermic at the induction of anesthesia; more commonly, their temperature decreases over time. The observation that recovery from vecuronium was slow during hypothermia suggests that in the clinical setting where mild hypothermia has developed during the course of the anesthesia, the clinician should anticipate that the duration of action of supplemental doses of vecuronium may prolonged. In addition, we stress the importance of monitoring neuromuscular function to detect any prolongation of neuromuscular blockade if hypothermia develops during the surgical procedure.

We were unable to detect any prolongation of neostigmine-induced recovery in the hypothermic patients. However, the number of patients studied was small, and so if a real difference existed, we may not have detected it. The fact that one hypothermic patient had markedly prolonged recovery, 35 min, suggests a potential for prolonged recovery during hypothermia. However, we can draw no firm conclusions as to the effect of hypothermia on neostigmine-induced recovery, except that further study is required.

Previously, we have demonstrated that adductor pollicis twitch tension is decreased approximately 15% per degree Celsius reduction in muscle temperature during isoflurane

anesthesia in the absence of muscle relaxants.[1] This effect was not a significant confounding factor in the current study because the twitch tension recorded at the time of administration of vecuronium was used as control twitch and because the body temperature changed <0.5° C during the measurement of the duration of action.

We did not insert needle thermocouples to measure adductor pollicis muscle temperature directly for two reasons. First, to do so is a relatively invasive procedure, involving risk of injury to the metacarpophalangeal joint and local nerve vascular supply. Second, because, in the absence of peripheral vasoconstriction, adductor pollicis muscle temperature closely follows central body temperature and is 0.5–1.0° C lower.[1] Because all of our patients were maintained at a central body temperature of >33° C (the predicted thermoregulatory threshold for peripheral vasoconstriction during nitrous oxide–isoflurane anesthesia[27]), we expected that peripheral vasoconstriction would not occur, and in fact none was observed.

In summary, the duration of action and recovery time for vecuronium-induced neuromuscular blockade are significantly prolonged during mild hypothermia in humans anesthetized with isoflurane and nitrous oxide.

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