Xenon does not modify mivacurium induced neuromuscular block

[Le xénon ne modifie pas le bloc neuromusculaire induit par le mivacurium]

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Purpose: The interaction between mivacurium and inhaled anesthetics is known, with the exception of xenon. We compared the pharmacodynamics of mivacurium during xenon anesthesia vs total *iv* anesthesia with propofol.

Methods: This randomized controlled trial was carried out in the Aachen University Hospital. Forty-two adult patients ASA I or II, aged 18 to 60 yr, were randomized to receive either xenon or propofol anesthesia. Anesthesia was induced with propofol and remifentanyl in both groups (each $n = 21$). The xenon group received xenon via facemask until an end-expiratory concentration of 60% was reached for one minute. Meanwhile, the acceleromyograph was calibrated and a train-of-four stimulation of the adductor pollicis muscle was started. After stabilization of the signal for five minutes, a single bolus of $0.16 \text{ mg} \cdot \text{kg}^{-1}$ mivacurium was injected. Anesthesia was maintained with xenon and remifentanyl or with propofol and remifentanyl.

Results: There were no significant differences between groups with respect to onset time (xenon 180 ± 64 vs propofol 195 ± 77 sec; $P = 0.39$), duration (xenon 16.18 ± 4.97 vs propofol 15.68 ± 6.17 min; $P = 0.73$), recovery index (xenon 5.63 ± 2.48 vs propofol 5.73 ± 2.12 min; $P = 0.42$) and clinical recovery (xenon 8.75 ± 2.57 vs propofol 9.28 ± 2.28 min; $P = 0.22$).

Conclusion: We conclude that the neuromuscular blocking effects of mivacurium are similar when given during propofol vs xenon anesthesia.

Objectif : L'interaction entre le mivacurium et les anesthésiques inhalés est bien connue, exception faite du xénon. Nous avons comparé la pharmacodynamie du mivacurium pendant l'anesthésie au xénon vs l'anesthésie exclusivement *iv* avec du propofol.

Méthode : L'essai randomisé et contrôlé a été mené au Aachen University Hospital. Quarante-deux patients adultes, d'état physique ASA I ou II, de 18 à 60 ans, ont reçu au hasard une anesthésie au xénon ou au propofol. L'induction a été faite avec du

propofol et du rémifentanyl chez les patients des deux groupes (chacun $n = 21$). Le xénon a été administré au masque jusqu'à une minute de concentration télé-expiratoire à 60 %. Entre-temps, l'accéléromyographe a été calibré et une stimulation en train-de-quatre de l'adducteur du pouce a été amorcée. Après un signal stable de cinq minutes, un bolus unique de $0.6 \text{ mg} \cdot \text{kg}^{-1}$ de mivacurium a été injecté. L'anesthésie a été maintenue avec du xénon et du rémifentanyl ou du propofol et du rémifentanyl.

Résultats : Il n'y a pas eu de différence intergroupe significative quant au délai d'installation du bloc (xénon 180 ± 64 vs propofol 195 ± 77 s; $P = 0.39$), à sa durée (xénon $16,18 \pm 4,97$ vs propofol $15,68 \pm 6,17$ min; $P = 0,73$), à l'indice de récupération (xénon $5,63 \pm 2,48$ vs propofol $5,73 \pm 2,12$ min; $P = 0,42$) et à la récupération clinique (xénon $8,75 \pm 2,57$ vs propofol $9,28 \pm 2,28$ min; $P = 0,22$).

Conclusion : Les effets neuromusculaires bloquants du mivacurium sont similaires pendant l'anesthésie au propofol ou au xénon.

THE combination of a short-acting opioid and neuromuscular blocking drug, such as remifentanyl and mivacurium, allow rapid emergence and recovery from anesthesia.¹ On the other hand, it is well known that most inhaled anesthetics variably prolong and enhance the effects of nondepolarizing neuromuscular blocking drugs, compared to total *iv* anesthesia.²⁻⁴ Xenon, a rediscovered inhaled anesthetic with an extremely low blood-gas solubility of 0.115 to 0.14⁵ and a minimum alveolar concentration (MAC) of 63 to 71%,^{6,7} has proven its clinical safety and efficacy in the past.⁸ With its ecological and pharmacological qualities, xenon is an interesting alternative to other inhaled anesthetics. The combination of a short-acting opioid, a short duration

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neuromuscular blocking drug such as mivacurium, and xenon may be of interest for fast-track anesthesia. It has been shown previously that xenon does not influence onset time, duration and recovery any differently than total *iv* anesthesia with propofol, following a single dose of $0.6 \text{ mg}\cdot\text{kg}^{-1}$ rocuronium.⁹ However, these observations with rocuronium (a monoquaternary steroid undergoing hepatic metabolism) may not be applicable to mivacurium (a benzyl isoquinoline derivative metabolized by pseudocholinesterase). Therefore, we investigated the hypothesis that xenon does not influence the nondepolarizing neuromuscular block induced by mivacurium after a single $2 \times \text{ED}_{95}$ dose.

Methods

With approval from the local Ethics Committee, 42 Caucasian adults (ASA I–II; Mallampati I–II; age 18–60 yr) were informed about the study and gave their written consent. The study was designed as a prospective randomized controlled trial based on the previously published "Good Clinical Research Practice (GCRP)" guidelines in a pharmacodynamic study of neuromuscular blocking drugs.¹⁰

Forty-two patients were assessed for eligibility and were randomized. Randomization was computer-generated and stratified by gender. Allocation concealment was ensured by enclosing assignments in sealed, sequentially numbered envelopes. The envelope was opened in the operating room before induction of anesthesia. In each group 21 patients were allocated to intervention. All received the allocated intervention. In the xenon group one patient was excluded from analysis, as the patient received further neuromuscular blocking agents due to surgical needs. In the propofol group one patient could not be analyzed due to a data transfer error. Patients were blinded, but blinding of the anesthesiologist and investigator was not possible because of the different routes of administration of the anesthetics (total *iv* anesthesia via infusion pump or inhaled anesthesia). Excluded were pregnant or breastfeeding women, patients with an expected difficult intubation, body weight more or less than 20% of ideal, any known allergies, use of medications known to interact with nondepolarizing neuromuscular blocking agents, or neuromuscular diseases.

Monitoring included electrocardiography, pulse oximetry, noninvasive blood pressure monitoring, capnography, end-tidal oxygen, and xenon determinations. The *iv* line and blood pressure cuff were placed on the arm contra-lateral to the neuromuscular monitoring.

Neuromuscular monitoring was performed using an acceleromyograph (TOF-Watch SX®, Organon

International, Roseland, NJ, USA), in accordance with GCRP guidelines¹⁰ and the manufacturer's instructions. Train-of-four (TOF) stimulation was used (supramaximal square wave impulse at 2 Hz every 15 sec, 200 μsec duration). Onset time was defined as the time of injection of mivacurium until 95% depression of the first twitch amplitude (T1) was reached. Duration T25 of neuromuscular recovery was defined as the beginning of injection of mivacurium to a 25% recovery of the first twitch. The recovery index T25–75 was defined as the time between 25% T1 and 75% T1 response of the TOF, and clinical recovery T25–0.8 as the time interval between T25 and a TOF ratio (T1/T4) of 0.8. Data were collected using the device specific accelograph software (TOF-Watch SX®, version 1.1).

Patients were premedicated with midazolam 7.5 mg orally, 45 min prior to induction. Anesthesia was induced intravenously with a single dose of propofol $2 \text{ mg}\cdot\text{kg}^{-1}$ and remifentanyl $0.5 \mu\text{g}\cdot\text{kg}^{-1}$ via an infusion pump, within 60 sec in both groups. Adjustments according to clinical needs were allowed (changes in blood pressure and heart rate more than $\pm 20\%$). Xenon administration was started via a facemask (xenon group). In the propofol group, the lungs were ventilated with oxygen/air (FiO_2 : 0.4). Xenon was administered using a closed circuit anesthesia machine (Physioflex®, Draeger, Lübeck, Germany) with modified software to reduce xenon consumption under minimal flow conditions.

Maintenance of anesthesia was achieved either by xenon (60% in O_2 reflecting a MAC value of approximately 0.95, referring to a MAC of 63% xenon) or propofol ($0.09\text{--}0.13 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, according to clinical needs), and remifentanyl was titrated to clinical needs in both groups. After an end-expiratory concentration of 60% xenon was attained, and in the propofol group after induction, the automatic set up procedure of the TOF-Watch was performed to determine the supramaximal stimulus. TOF monitoring was started and, after stabilization of the signal for five minutes, mivacurium $0.16 \text{ mg}\cdot\text{kg}^{-1}$ ($2 \times \text{ED}_{95}$) was injected within five seconds. Intubation of the trachea was performed after the first twitch of the TOF reached 5% of control. Ventilation was adjusted to maintain an end-expiratory carbon dioxide concentration at 32 to 40 mmHg. Complete spontaneous recovery of neuromuscular block was attained in all patients before the end of surgery, and therefore, the anesthetic state was attained in all patients during the full spontaneous recovery period from neuromuscular blockade. No patient required an additional dose of neuromuscular blocking drug or pharmacological antagonism.

TABLE I Characteristics of patients

	<i>Xenon</i>	<i>Control</i>
Age (yr)	38 ($\pm$ 11)	41 ($\pm$ 13)
Sex (female/male)	12/8	12/8
Height (cm)	170.0 ($\pm$ 9.0)	171.8 ($\pm$ 10.1)
Weight (kg)	68.0 ($\pm$ 13.0)	72.1 ($\pm$ 14.0)

Values are mean ($\pm$ SD).

TABLE II Neuromuscular monitoring

	<i>Xenon</i>	<i>Control</i>	<i>P values</i>
Onset time	165 (135-225); 180 [$\pm$ 64]	165 (143-240); 195 [$\pm$ 77]	0.39
T ₂₅	14.63 (13.25-18.13); 16.18 [$\pm$ 4.97]	16.0 (11.75-16.75); 15.68 [$\pm$ 6.17]	0.73
T ₂₅₋₇₅	5.5 (3.38-6.75); 5.63 [$\pm$ 2.48]	5.25 (4.13-6.97); 5.73 [$\pm$ 2.12]	0.42
T _{25-TOFR 0.8}	8.75 (7.0-10.0); 8.75 [$\pm$ 2.57]	9.5 (7.63-10.38); 9.28 [$\pm$ 2.28]	0.22

TOFR = train-of-four ratio. Onset time in seconds, duration T25, recovery index T25-75 and clinical recovery T25-TOFR 0.8 of mivacurium ($2 \times \text{ED}_{95}$) in minutes. Values in median (interquartile range); mean ($\pm$ SD).

Sample size was calculated with a power of $\beta = 0.8$ and a significance level of $\alpha = 0.05$, considering a clinically important difference of 20% in the recovery index as relevant. Mean values and standard deviation were taken from the onset time of our previous study analyzing neuromuscular effects of rocuronium.⁹ The sample size was estimated to be 21 patients in each group, including four additional patients to account for dropouts.

Demographic data were analyzed for homogeneity. Onset-time T5, duration T25, recovery index T25-75 and clinical recovery T25-0.8 are presented as mean, standard deviation, median, and interquartile range. Data were analyzed using a two-sided rank sum Wilcoxon test. Statistical analysis was performed using SAS software version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 40 patients completed the protocol. The groups were comparable with respect to age, sex distribution, height and body weight (Table I). Anesthesia was induced with propofol $2.1 \pm 0.28 \text{ mg}\cdot\text{kg}^{-1}$ and remifentanyl $0.47 \pm 0.06 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ (mean $\pm$ SD) in the xenon group and $2.05 \pm 0.17 \text{ mg}\cdot\text{kg}^{-1}$ and $0.45 \pm 0.06 \text{ }\mu\text{g}\cdot\text{kg}^{-1}$ in the propofol group ($P = 0.74$; $P = 0.23$). Hemodynamic variables remained stable, and normothermia ($35.5\text{--}37^\circ\text{C}$) was maintained by

use of warming blankets. The maintenance xenon concentration was $60.7 \pm 2.4\%$ while the mean propofol infusion rate was $0.11 \pm 0.02 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The remifentanyl infusion rate was $0.2 \pm 0.11 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the xenon group and $0.2 \pm 0.10 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the propofol group ($P = 0.51$).

The neuromuscular effects of mivacurium were not different between groups (Table II). No adverse events were observed during the course of the study.

Discussion

Our data confirm the hypothesis that xenon does not modify the effects of a single dose ($2 \times \text{ED}_{95}$) of mivacurium, when compared with propofol. There were no differences in onset time, duration, recovery index and recovery.

Acceleromyography with TOF stimulation was used for neuromuscular monitoring according to GCRP guidelines for phase III studies.¹⁰ However, it is important to take into account variations of each method of neuromuscular monitoring (acceleromyography, mechanomyography and electromyography) and results from different methods shouldn't be compared.^{11,12}

The short equilibration time used in this study may be considered a possible disadvantage of our study design. Some demand a 30 to 40 min equilibration period of the muscular compartment when using inhaled anesthetics with a high blood-gas solubility, particularly for determination of infusion rates of neuromuscular blocking drugs.¹³ Xenon has the lowest blood-gas solubility of all inhaled anesthetics by a wide margin. The solubility of volatile anesthetics in muscle is influenced by body temperature and the patient's age. Solubility of xenon in muscle is 0.082, and thus extremely low compared to values for middle aged adults for halothane (1.44 ± 0.17), enflurane (1.09 ± 0.10), isoflurane (1.52 ± 0.11), sevoflurane (1.08 ± 0.20), desflurane (0.62 ± 0.06), or nitrous oxide (0.54).¹⁴⁻¹⁶ Based upon these data, it can be assumed that equilibration of xenon in the muscle compartment is complete when a steady state end-expiratory concentration has been achieved.

We planned this study without measuring the pseudocholinesterase activity, since it is not measured routinely in the preoperative screening of patients. Furthermore, plasma cholinesterase, responsible for the metabolism of mivacurium¹⁷ is not inhibited by either propofol or xenon.¹⁸ No patient showed an unusual prolongation of recovery, suggesting pseudocholinesterase deficiency.

Previous studies by Kunitz⁹ and Nakata¹⁹ support our results. Nakata *et al.* demonstrated that 57%

xenon had less influence on a vecuronium induced neuromuscular block, when compared with 1.6% sevoflurane. Onset times were similar, but 25% recovery of T1 was longer in the sevoflurane group (acceleromyography). T25–75 and T0.8 values were not measured.¹⁹

Kunitz and coworkers measured onset times, duration and recovery after a single bolus of 0.6 mg·kg⁻¹ rocuronium, using an identical protocol to ours. There were no significant differences between groups with respect to onset time, duration, recovery index and clinical recovery.⁹

The use of inhaled anesthetics with a low blood-gas solubility such as xenon facilitate more rapid emergence and recovery. The combination of a short-acting opioid and a neuromuscular blocking drug of short duration, such as remifentanyl and mivacurium, seem to be a reasonable combination to facilitate a rapid recovery from general anesthetic. In contrast to other inhaled anesthetics, xenon does not prolong neuromuscular blockade after a single dose of mivacurium.

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