Anesthesiology
74:474–478, 1991

# *Effects of Residual Concentrations of Isoflurane on the Reversal of Vecuronium-induced Neuromuscular Blockade*

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**Thirty-six anesthetized patients (ASA physical status 1 or 2) undergoing elective surgery were monitored (isometric adductor pollicis mechanical activity) to detect the effects of discontinuing isoflurane anesthesia upon the reversal of vecuronium-induced neuromuscular blockade. Neuromuscular blockade was produced by vecuronium 100 μg/kg and additional doses of 20 μg/kg until completion of surgery. The patients were randomly divided into three groups: in the control group (n = 12), only fentanyl/$N_2O$ was given; in the "isostable" group (n = 12), isoflurane at an end-tidal concentration of 1.25% was maintained throughout anesthesia; in the "isostop" group (n = 12), isoflurane 1.25% was discontinued before neostigmine administration. In all groups, paralysis was antagonized with 15 μg/kg intravenous (iv) atropine and 40 μg/kg iv neostigmine when the twitch height (0.1 Hz) had regained 25% of its control value. The measured parameters were twitch height, train-of-four, and 50–100-Hz tetanic fade. No significant differences were found among the three groups with respect to the final twitch heights and tetanic fades at 50 Hz. In the isostable group, final mean train-of-four was significantly less (75%) than in the other patients (88%) ($P < 0.01$). Mean tetanic fade at 100 Hz was significantly less in the isostable group (31%) than in the isostop group (57%) ($P < 0.01$) and control group (84%) ($P < 0.01$). We conclude that discontinuing isoflurane anesthesia for 15 min improves the reversal of a vecuronium paralysis. In addition, after the antagonism of vecuronium-induced neuromuscular blockade, tetanic fade at 100 Hz appears useful to detect the slight impairment of the neuromuscular transmission that is induced by residual isoflurane concentrations and that is undetected by train-of-four measurements. (Key words: Anesthetics, volatile: isoflurane. Antagonists, neuromuscular relaxants: neostigmine. Neuromuscular relaxants: vecuronium. Neuromuscular transmission, tests: twitch height, train-of-four, tetanic fade.)**

THE IMPAIRMENT OF NEUROMUSCULAR TRANSMISSION produced by nondepolarizing blocking agents is enhanced to a varying degree by various halogenated anesthetics.[1–4] This enhancement of neuromuscular blockade seems to be concentration-dependent. Furthermore, maintenance of anesthesia with enflurane or isoflurane can substantially impede antagonism of nondepolarizing agents by anticholinesterases.[5,6]

In this study, we investigated the discontinuation of isoflurane after reversal of a vecuronium-induced neuromuscular blockade by a fixed atropine–neostigmine dose given at a precise prereversal twitch height. The effect of the anticholinesterase treatment was observed in three different conditions: first, in the absence of halogenated anesthetics; second, in the presence of sustained end-tidal isoflurane concentration; and finally, 15 min after isoflurane discontinuation at the end of a sustained isoflurane anesthesia.

The residual neuromuscular transmission was assessed with various frequencies of neural stimulation: as previous clinical work has shown, even with a train-of-four ratio in the range of 0.75, frank impairment of the neuromuscular transmission can be detected with high-frequency tetanic stimulation.[6]

## Materials and Methods

Thirty-six patients (ASA physical status 1 or 2) undergoing elective surgery were studied after their informed consent was obtained. The study was approved by the hospital ethical committee for human research (Research Committee, Brussels Free University). None of the patients had clinical or routine biochemical evidence of hepatic or renal damage. All were free from neuromuscular disease and drugs that may interfere with the neuromuscular junction function. Demographic details of the patients included in this study are showed in table 1.

The patients received 0.2 mg/kg diazepam orally 1 h before anesthesia. The following catheters were inserted under local anesthesia: one (18-G Surflo®) peripheral venous catheter into the left cubital vein and one arterial catheter in the right radial artery (20-G Leadercath®). Anesthesia was induced with thiopental 3–5 mg/kg intravenously (iv). After loss of consciousness, ventilation was controlled manually (50% $O_2$ in $N_2O$) until the trachea was intubated, after the administration of vecuronium. Thereafter, ventilation was controlled mechanically until the end of the surgical procedure (open circuit, 35% $O_2$ in $N_2O$). Ventilation was adjusted to produce normocapnia (end-tidal $CO_2$ tension about 5.0 ± 0.1%, or arterial

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Received from the Departments of Anesthesiology and of Intensive Care Medicine, University Hospital Erasme and the Department of Anesthesiology, University Hospital Brugmann, Free University of Brussels (Université Libre de Bruxelles), Brussels, Belgium. Accepted for publication November 27, 1990.

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TABLE 1. Patient Demographic Data

| | Control | Isostable | Isostop |
|---|---|---|---|
| Age (yr) | 41.6 ± 6.9 | 39.9 ± 1.8 | 42.9 ± 1.6 |
| Weight (kg) | 65.4 ± 2.8 | 66.7 ± 4.1 | 66.2 ± 2.0 |
| Height (cm) | 168.5 ± 1.3 | 164.1 ± 2.4 | 162.7 ± 1.8 |
| Vecuronium consumption ($\mu g \cdot kg^{-1} \cdot min^{-1}$) | 0.62 ± 0.09 | 0.79 ± 0.06 | 0.66 ± 0.08 |

Results are expressed as mean ± SEM.

$CO_2$ tension [$Pa_{CO_2}$] between 35 and 39 mmHg). A central venous catheter was then inserted into the superior vena cava *via* the right internal jugular vein (16-G Leadercath®).

A force-displacement transducer (UC3 cell, Statham), fitted with a tension attenuator (UL4-20, Statham) and incorporated in a hand grip, was secured with adhesive tape in the patient's left hand to measure isometric contraction of the adductor pollicis. After induction of anesthesia, two pediatric surface electrodes were placed near the ulnar nerve at the wrist. Mechanical activity was induced in the adductor pollicis by square-wave pulses of 0.2-ms duration at supramaximal intensity, delivered at 0.1 Hz from a Bard S 88 stimulator. The resulting analog signals were amplified and registered on a polygraph recorder. After a 3-min recording of control twitch height, vecuronium 100 $\mu$g/kg was given iv, and the trachea was intubated once the twitch height decreased to 5% of its initial value. Every time until the end of surgery that twitch height regained 25% of its baseline height, vecuronium 20 $\mu$g/kg was given.

For maintenance of anesthesia, the patients were randomly divided into three groups of 12 patients each. In the first group (control), the patients received 5 $\mu$g/kg fentanyl iv and 100 $\mu$g/kg dehydrobenzperidol iv, followed by reinjections of 2 $\mu$g/kg fentanyl iv when clinical evidence of inadequate analgesia was observed. In the second group ("isostable"), isoflurane at an end-tidal concentration of 1.25% was given until the end of anesthesia. In the third group ("isostop"), isoflurane was given at an end-tidal concentration of 1.25% and was terminated 2 min before reversal of vecuronium paralysis. End-tidal concentrations of the anesthetics were measured with a piezoelectric detector placed in the expiratory limb of the circle circuit (Servo Gas Monitor, Siemens). The apparatus was calibrated before each clinical session with the calibration device provided by the manufacturer and with reference halogenated anesthetics in $N_2O$ and $O_2$ 2:1 ratio mixtures. The end-tidal isoflurane anesthetic concentration of 1.25% represents approximately 1 MAC.[7]

Because of the physical properties of isoflurane,[8,9] the attainment of sufficient equilibration between blood and muscle isoflurane partial pressures required that the surgical procedures last at least 90 min to ensure a consistent potentiating effect of isoflurane upon the neuromuscular junction. (More than 1 h was advocated by Stanski *et al.*,[10] Saidman,[11] and Driessen *et al.*[12])

Heat loss from the body surface and the exposed left arm was controlled with a warming mattress (37° C) and surgical sheets. Plasma $K^+$, $Na^+$, and $Ca^{++}$ were measured every 30 min from heparinized blood samples and maintained within normal values with iv infusion when necessary.

To determine isoflurane blood concentrations by the double extraction method,[13–15] heparinized blood samples were taken simultaneously from ipsilateral arterial and peripheral venous sites, and from the superior vena cava, 3 min before and 16 min after neostigmine administration, when tetanic stimulations were achieved.

Vecuronium paralysis was antagonized with 40 $\mu$g/kg neostigmine and 15 $\mu$g/kg atropine iv when twitch tension returned to 25% of the control twitch height. After administration of the atropine–neostigmine mixture, the following variables were observed during a 15-min period in order to document the relative sensitivity of these tests for the detection of the residual impairment of the neuromuscular transmission: twitch height every 10 s and train-of-four (2 Hz) every 3 min. Immediately thereafter, tetanic fade (100 and 50 Hz, 5-s duration, at 1-min intervals) were assessed sequentially in random fashion. The degree of tetanic fade was calculated as the ratio between residual muscular activity observed after 5 s of stimulation and the maximal response registered.

To compare the possible effect of the different anesthetics received by the three groups of patients upon the vecuronium requirement, vecuronium consumption was determined as follows: the total dose of vecuronium minus the loading dose was divided by the time elapsed between the first reinjection and the administration of the atropine–neostigmine mixture.

Statistical analysis of the data was performed with one-way analysis of variance or Wilcoxon's test, according to Statistical Program for Social Sciences package programs.[16] The statistical comparisons were considered significant at the $P < 0.05$ level.

## Results

There were no significant differences among the patients with regard to age, weight, height, and vecuronium consumption (table 1).

The final mean twitch height recoveries were similar among the three groups and were greater than 95% (no significant differences).

Figure 1 illustrates the evolution of the trains-of-four observed in the different groups. Before neostigmine administration, the mean train-of-four ratio was 7% in the control group, 8% in the isostable group, and 10% in the isostop group (no significant difference). Fifteen minutes after atropine–neostigmine administration, a train-of-four value of 88 ± 2% (mean ± SEM) were observed in both the control and the isostop groups. These values were significantly greater than the mean train-of-four value in the isostable group, 75 ± 2% ($P < 0.01$).

For the 50-Hz, 5-s stimulation tests, there were no significant differences among the three groups and all were above 85% (fig. 2). At 100 Hz, the mean value of the control group, 84%, was significantly greater than the values of 31% ($P < 0.01$) and 57% ($P < 0.01$) recorded in the isostable and the isostop groups, respectively.

Table 2 gives the arterial, venous, and superior vena cava isoflurane concentrations measured in the isostop and isostable groups, measured 3 min before (no significant differences between the two groups) and 16 min after neostigmine administration. At the last sampling period, mean end-tidal isoflurane was 1.25% in the isostable group but 0.17% in the isostop group ($P < 0.001$, Wilcoxon's test).

## Discussion

It is well established that after administration of nondepolarizing neuromuscular blocking agents, volatile anesthetics may have an additional depressant effect on neuromuscular transmission.[3,17] In the absence of neuromuscular relaxants, impairment of neuromuscular transmission can be detected only if the isoflurane end-tidal concentration exceeds 1 MAC and if a stimulation rate greater than 120 Hz is used.[18]

During reversal of neuromuscular blockade, enflurane[5,6] and isoflurane[6] can impede the antagonism of nondepolarizing neuromuscular blocking agents[5,6] if train-of-four[5,6] or tetanic stimulation rates are used.

Only a few data were available concerning the role of residual concentrations of volatile anesthetics upon the antagonism of neuromuscular blockade obtained by anticholinesterases. Therefore, this study was designed to observe and to compare reversal of vecuronium-induced neuromuscular blockade after atropine–neostigmine in patients without and in the presence of approximately 1 MAC isoflurane end-tidal concentration (1.25%) or 15 min after discontinuation of isoflurane administration. Among the tests used to ascertain neuromuscular transmission, no significant differences were observed among the three groups of patients if final twitch height or tetanic fade 50-Hz measurements were considered. For the train-of-four recordings, the mean train-of-four ratio observed 15 min after isoflurane discontinuation (*i.e.*, in isostop patients) was identical to the value observed in the patients receiving no halogenated anesthetic. On the other hand, in patients in whom anesthesia was maintained with 1.25% isoflurane, the final mean train-of-four ratio remained depressed to 75% ($P < 0.01$). With high tetanic stimulation rates (*e.g.*, 100 Hz), residual impairment of neuromuscular

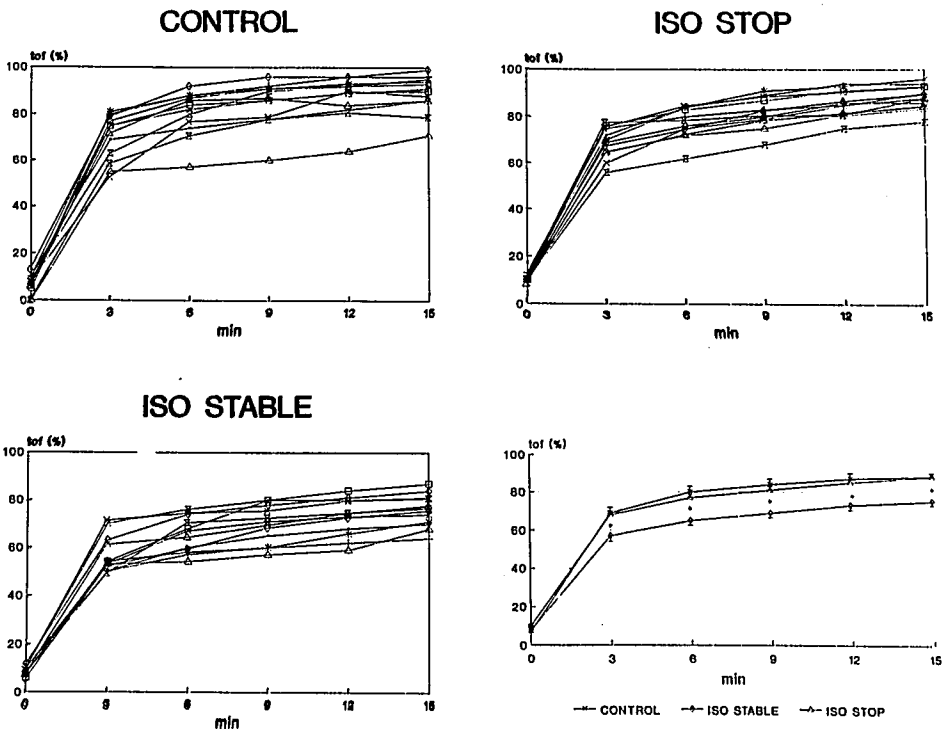


FIG. 1. Evolution of train-of-four recorded at 3-min intervals after administration of 40 μg/kg neostigmine once the twitch height level regained 25% of its initial value. Control, n = 12; isostop, n = 12; isostable, n = 12. *Bottom right:* mean ± SEM; *$P < 0.01$, one-way analysis of variance.

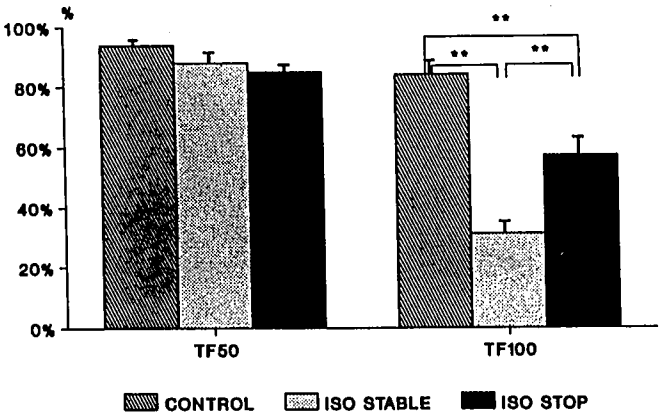


FIG. 2. Values of the tetanic fade recorded 15 min after administration of 40 μg/kg neostigmine. Stimulation rates: 50 Hz (*left*) and 100 Hz (*right*). $^{**}P < 0.01$, one-way analysis of variance.

transmission in the different groups appeared more pronounced: 84, 57, and 31% were observed for the control, isostop, and isostable groups, respectively.

The differences observed between the response to train-of-four stimulation and tetanic fade after 100-Hz stimulation were due not solely to the presence of halogenated anesthetics.[6] Other studies have shown these differences after vecuronium at the beginning of spontaneous paralysis reversal[19] or in presence of therapeutic plasma concentrations of disopyramide.[20]

Fifteen minutes after its discontinuation, isoflurane end-tidal, arterial, and venous concentrations had decreased markedly (table 2): venous concentration had decreased by a factor of 4 and arterial concentration by a factor of 8. However, these reductions were not sufficient to eliminate the residual effects of isoflurane upon the neuromuscular transmission and the contraction of the adductor pollicis elicited at 100 Hz. In other words, as a consequence of the muscle–blood isoflurane partition coefficient of 3.4 and relatively low muscle blood flow, even after 15 min, sufficient isoflurane remained in the muscle to affect muscle response to nerve stimulation.

Should larger doses of antagonists be used when reversing neuromuscular blockade in patients receiving volatile anesthetics? Isoflurane has been shown to produce a dose-dependent "flickering" of the nicotinic acetylcholine-activated ion channel, causing the channel to fluctuate rapidly between the open and closed states under conditions in which a drug-free channel would otherwise remain open.[17] Consequently, isoflurane potentiation of neuromuscular blockade induced by nondepolarizing muscle relaxants appears to be a noncompetitive phenomenon. Under these conditions, this kind of potentiation would be only poorly reversible with classical anticholinesterase agents.

Previously, the ability to sustain head lift for 5 s or to produce negative pressure greater than $-25$ cm$H_2O$ were considered as acceptable criteria for clinical recovery[21,22] in patients after anesthesia of either opioid in $N_2O$ or halogenated anesthetics in $N_2O$ once the train-of-four ratio regained values above 70%. More recently, however, Pavlin *et al.*[23] observed that despite the fulfillment of these criteria, in unanesthetized volunteers, the muscles responsible for the airway protection were still partially paralyzed.

Commenting in an editorial on the observations of Pavlin *et al.*, Miller[24] underlines the necessity to find more sensitive indices of the adequacy of reversal of neuromuscular blockade. It is clear that with a cooperative patient the correct execution of a 5-s sustained head lift can be accepted as the "clinical gold standard."[23,24] In the anesthetized patient, however, tests more sensitive than twitch height, tetanic fade after 50-Hz stimulation, and response to train-of-four stimulation may be needed.

To confirm that tetanic fade after 100-Hz stimulation[25] may represent a more sensitive index for detection of residual neuromuscular impairment, studies correlating the differences in response to 100-Hz stimulation with clinical end points (such as the hand grip test, the head lift test, or the parameters studied by Pavlin *et al.*[23]) are indicated. It is noteworthy that a 100-Hz stimulation rate is already available in a great number of the commercially available nerve stimulators.

In conclusion, although a 15-min discontinuation of isoflurane can favorably affect the antagonism of a vecuronium-induced paralysis, it was not sufficient to obtain

TABLE 2. Isoflurane Concentrations in Heparinized Blood Samples

| Time | Sampling Site | Isoflurane Concentration ($\times 10^{-9}$ M) | |
|---|---|---|---|
| | | Isostable | Isostop |
| Before vecuronium antagonism | Radial artery | 283.5 ± 15.2 | 315.4 ± 12.5 |
| | Vena cava superior | 237.4 ± 16.3 | 266.1 ± 14.6 |
| | Forearm vein | 220.0 ± 11.4 | 269.4 ± 10.8 |
| 16 min after atropine/ neostigmine administration | Radial artery | 274.8 ± 11.4 | 36.9 ± 3.2* |
| | Vena cava superior | 231.4 ± 14.1 | 68.3 ± 4.9* |
| | Forearm vein | 250.4 ± 13.6 | 65.6 ± 6.0* |

Results are expressed as mean ± SEM.

* Statistically significant differences ($P < 0.01$).

a reversal pattern comparable to that observed in patients anesthetized with fentanyl in $N_2O$ and $O_2$. The future use of less soluble inhaled anesthetics such as sevoflurane or desflurane may further reduce the differences seen with isoflurane in the current study. Clinically, it should be kept in mind that, despite a measured end-tidal isoflurane concentration of less than 0.2%, residual isoflurane concentrations present 15 min after anesthetic discontinuation may interfere with the antagonism of vecuronium neuromuscular blockade.

The authors wish to thank Mrs. Michele Stiennon and Ms. Michele Geeraerts for secretarial help.

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