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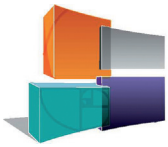

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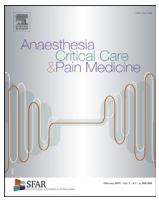

Original Article

Under sevoflurane anaesthesia, a reduced dose of neostigmine can antagonize a shallow neuromuscular block: A double-blind, randomised study

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ABSTRACT

Background: It has been demonstrated that small doses of neostigmine (10–30 μg.kg^{-1}) effectively antagonize atracurium blocks at a train-of-four (TOF) ratio of 0.4 under propofol anaesthesia. The results might not be valid with halogenated agents, which potentiate neuromuscular blockades. The goal of this study was to determine the dose of neostigmine required to antagonize a block corresponding to a TOF ratio of 0.4, a level at which fade is not visually detected.
Methods: Sixty patients were included and anaesthesia was induced with propofol, remifentanil and cisatracurium, and maintained with sevoflurane and remifentanil. Patients were randomized to receive neostigmine at 40, 20, 10 μg.kg^{-1} or placebo with atropine (20, 10, 5 or 0 μg.kg^{-1}, respectively) as soon as the TOF ratio reached 0.4. Elapsed times to 0.9 and 1.0 TOF ratios were measured.
Results: The median times elapsed from 0.4 to 0.9 and 1.0 TOF ratios in the placebo group were 19 (10.5–36) min and 26 (20–50) min, respectively, and significantly shorter (I = 0.002) with any dose of neostigmine than without. Times for complete recovery after 40 and 20 μg.kg^{-1} neostigmine were similar [5.5 (4–11) min and 7.8 (3.5–11) min, respectively] but significantly shorter than after 10 μg.kg^{-1} neostigmine [17 min (7–55); I = 0.001].
Conclusion: Under sevoflurane anaesthesia, in absence of tactile or visual TOF fade, which corresponds to a TOF ratio ≥ 0.4, 20 μg.kg^{-1} neostigmine is as effective as 40 μg.kg^{-1} in antagonizing shallow cisatracurium block.

1. Introduction

Residual paralysis [i.e. a mechanographic train-of-four (TOF) ratio < 0.9] remains frequent [1,2] and is potentially harmful [3–5]. Below this threshold, adverse events, such as upper airway obstruction, aspiration, respiratory depression and hypoxaemia, may occur and lead to potential morbidity [6–12]. Debaene et al. showed that two hours after a single intubation dose of neuromuscular blocking agent without reversal, 37% of patients had residual paralysis and upon arrival in the post anaesthetic care unit, most of them had a TOF ratio ≥ 0.4 [1], a level of paralysis that is impossible to detect without quantitative measurement of the TOF ratio. Absence of TOF fade with visual and tactile evaluation corresponds to a TOF ratio between 0.4–1.0 [13]. Thus, shallow neuromuscular blocks, corresponding to a TOF ratio in the range 0.4–0.9, should be antagonized.

Concerns have been raised about neostigmine-induced neuromuscular weakness when given to antagonize shallow blocks [14–16]. Also, the cardiovascular effects of neostigmine are dose-dependent, so there might be advantages in giving relatively lower doses of neostigmine when recovery is almost complete. Reduced doses of neostigmine (10–30 μg.kg^{-1}) were effective in antagonizing shallow atracurium blocks in propofol anaesthesia [17]. These results might not be valid with halogenated agents, which potentiate neuromuscular blockades [18]. The goal of this study was to determine, under sevoflurane anaesthesia, whether a reduced dose of neostigmine could effectively antagonize residual paralysis at a TOF ratio of 0.4, a level at which fade is not visually detected.

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2. Patients and methods

The study protocol was approved by the Research Ethics Committee of the Nantes University Hospital and took place in the Centre Hospitalier Départemental, La Roche-sur-Yon, France. All patients gave written informed consent. This trial was registered with clinicaltrials.gov (NCT00847938). We studied 64 American Society of Anesthesiologists (ASA) physical status I-III adults scheduled for elective surgery (digestive, urologic, gynaecological, orthopaedic or ENT surgery) under general anaesthesia with tracheal intubation and with no need of cisatracurium reinjection. Exclusion criteria were: age < 18 years or > 75 years, neuromuscular, hepatic or renal disease, unstable coronaropathy, severe asthma, glaucoma, urinary obstruction, pregnancy, body mass index (BMI) > 32 kg.m^{-2}, suspected difficult tracheal intubation, allergy to drugs used in the study, and using or being on a medication that interferes with neuromuscular function. Sixty-two patients were randomly divided into four groups: when the acceleromyographic TOF ratio had recovered to 0.4, they received, in a double-blind manner, 40, 20, 10 μg.kg^{-1} of neostigmine or placebo with respectively 20, 10, 5 μg.kg^{-1} of atropine or placebo. Heart rate, noninvasive arterial blood pressure, BIS, sevoflurane expired fraction and TOF ratio were documented every minute until complete recovery (i.e. TOF ratio ≥ 1).

2.1. Induction and maintenance of anaesthesia

Patients were orally pre-medicated with hydroxyzine 1 mg.kg^{-1}. Monitoring included electrocardiography, noninvasive arterial blood pressure, pulse oxymetry, capnography, bispectral index (BIS) and a temperature probe. Central temperature was maintained over 35 °C using a warming blanket covering the upper body and both arms. Anaesthesia was induced using a target control infusion (TCI) device with the effect concentrations of remifentanil set between 2 and 6 ng.mL^{-1} and a bolus of propofol 1.5 to 3 mg.kg^{-1}. After 0.1 mg.kg^{-1} of cisatracrurium, tracheal intubation was performed. Anaesthesia was maintained with remifentanil (TCI, 1–8 ng.mL^{-1} effect concentration) and sevoflurane (1–2.5% expired fraction), with nitrous oxide/oxygen (50%/50%) to maintain BIS between 40 and 60. There was no cisatracurium reinjection during the surgical procedure. The patients' lungs were ventilated and the end-tidal partial pressure for carbon dioxide was maintained between 32 and 36 mmHg.

2.2. Neuromuscular monitoring

Neuromuscular blockade was monitored with acceleromyography (TOF-Watch SX™, Organon Int., Dublin, Ireland). Two ECG electrodes were applied to the ulnar nerve at the wrist of a dominant or non-dominant extremity and a TOF-Watch SX™ nerve stimulator was used for supramaximal TOF stimulation (4 pulses of 0.2 ms in duration at a frequency of 2 Hz every 15 s). The acceleration transducer of the acceleromyography was fixed to the volar side of the distal phalanx of the thumb on a small elastic hand adapter applying a constant preload (TOF-Watch Handadapter™, Organon Int.). After anaesthesia induction, the TOF-Watch SX™ was calibrated using the calibration mode 2. Then, cisatracrurium 0.1 mg.kg^{-1} was given and orotracheal intubation was performed. When the TOF ratio recovered to 0.4, the patient randomly received 40, 20, 10 μg.kg^{-1} neostigmine, or placebo with 20, 10, 5 μg.kg^{-1} of atropine or placebo, respectively. Sevoflurane, nitrous oxide and neuromuscular monitoring were continued until at least two TOF ratio measurements exceeded 1.0. The times (min) elapsing from a TOF ratio of 0.4 to 0.9 and from 0.4 to 1.0 after administration of neostigmine or placebo were noted.

2.3. Randomization and statistical analysis

Study subjects were randomly allocated in a double-blind fashion. Randomisation was performed initially according to a computer-generated randomisation schedule (in blocks of 4) without stratification. Atropine and neostigmine were mixed into the same syringe by an anaesthetist not in charge of the patient with saline to obtain 20 mL according to predetermined randomisation. Placebo was normal saline in a 20 mL syringe. Data [heart rate, pulse oxymetry, capnography, bispectral index (BIS), and TOF ratio] were collected every minute from a TOF ratio of 0.4 to 1.0 and every five minutes for noninvasive arterial blood pressure by the anaesthetist in charge of the patient and unaware of the patient's randomisation.

The primary outcome was the recovery time to 1.0, defined as time from the injection of neostigmine or placebo (TOF ratio = 0.40) to recovery of a TOF ratio of 1.0. The recovery time to a TOF ratio of 0.9 was considered as a secondary outcome.

A decrease of 10 minutes for the recovery time was considered to be clinically significant. Previous studies gave a standard deviation of 8 min. Thus, the number of patients needed per group was 15 ($\alpha = 0.05$ and $1\text{-}\beta = 0.8$). The percentage of patients with complete reversal (i.e. TOF ratio ≥ 1.0) within 5 and 10 minutes was calculated. TOF results were expressed as medians and ranges.

Recovery time to 1.0 was compared among groups using Analysis of Variance (ANOVA). When ANOVA detected differences between groups, a Tukey test was performed to pinpoint those groups that were significantly different. Patient characteristics were expressed as means ± standard deviations or absolute numbers, as appropriate, and were compared using Mann-Whitney-U tests. A value of $P < 0.05$ was considered as statistically significant.

3. Results

We screened 64 patients, who all met inclusion criteria between March and November 2009. Two patients declined to participate and 62 were randomly assigned. For 2 patients (3%), no data were collected because of equipment breakdown (Fig. 1). Patient characteristics (age, BMI, sex distribution, ASA, time of surgical procedure) are presented in Table 1. No significant differences among the groups were found. The TOF ratio before cisatracurium injection and after calibration was 1.07 ± 0.06. The interval between cisatracurium injection and a TOF ratio of 0.4 was 62.5 ± 11.5 min. At the injection of neostigmine or placebo, the TOF ratio was 0.41 ± 0.01 and the mean sevoflurane expired fraction was 0.98 ± 0.25%. A TOF ratio ≥ 1.0 was attained in all 60 patients during the recovery from neuromuscular blockade.

Times from 0.4 to 0.9 and from 0.4 to 1.0 TOF ratios were significantly shorter with any dose of neostigmine than without ($P < 0.05$) (Table 2). Recovery times were not different between the 40 and 20 μg.kg^{-1} groups, but the latter were significantly shorter than with 10 μg.kg^{-1} neostigmine or placebo (Table 2). The proportions of patients reaching a TOF ratio of 1.0 within 10 minutes for the 40, 20 and 10 μg.kg^{-1} neostigmine groups were respectively 94%, 86%, 27%. No patient in the placebo group reached a TOF ratio > 0.9 within 10 minutes (Fig. 2). All patients in the 40 and 20 μg.kg^{-1} neostigmine groups reached a TOF ratio of 1.0 in 11 minutes.

After atropine and neostigmine, tachycardia was observed in the groups receiving 40 μg.kg^{-1} neostigmine with 20 μg.kg^{-1} atropine and 20 μg.kg^{-1} neostigmine with 10 μg.kg^{-1} atropine, with a 64% and 50% increase in heart rates (HR), respectively, compared with the pre-injection value ($P > 0.05$). In the 10 μg.kg^{-1} neostigmine group with 5 μg.kg^{-1} atropine, only a