Parasympathetic nervous activity after administration of atropine and neostigmine using heart rate spectral analysis

KEN-ICHI IWASAKI1,2, HAJIME SUZUKI1, SHIGERU SAEKI1, KIYOSHI MASE1, SETSURO OGAWA1, KANAME HIRAYANAGI2, and KAZUYOSHI YAJIMA2

Department of Anesthesiology, Surugadai Nihon University Hospital, 1-8-13 Kanda-Surugadai, Chiyoda-ku, Tokyo 101, Japan
2Department of Hygiene, Nihon University School of Medicine, 30-1 Ohyaguchi-Kaminachi, Itabashi-ku, Tokyo 173, Japan

Abstract: Recently, heart rate spectral analysis has become recognized as a powerful tool for quantitatively evaluating autonomic nervous system activity. The purpose of this study was to analyze parasympathetic nervous activity by heart rate spectral analysis after administration of atropine and neostigmine for reversal of residual neuromuscular blockade. For our study, 36 female patients (26-37 years of age), ASA physical status (PS) I, who were scheduled for laparoscopic examination, were randomly allocated to one of the following four groups: In group A (1:1), 9 patients received 1.0mg atropine followed 4 min later by 1.0mg neostigmine. In group B (1:2), 9 patients received 0.5mg atropine followed 4 min later by 1.0mg neostigmine. In group C (1:2.5), 9 patients received 1.0mg atropine followed 4 min later by 2.5mg neostigmine. In group D (1:2mix), 9 patients received a mixed solution of atropine 0.5mg and neostigmine 1.0mg. After finishing the laparoscopic examination, additional anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0.5% isoflurane. The control data were obtained 10 min after finishing the laparoscopic examination. After that, the data on atropine were obtained between 2 and 4 min after administration of atropine, and the data on neostigmine were obtained between 5 and 7 min after administration of neostigmine. We selected power spectral density of the high-frequency component (HF-p) in heart rate spectral analysis as an index to assess parasympathetic activity. In groups A, B, and C, the HF-p decreased after administration of atropine. In groups B and C, the HF-p increased after administration of neostigmine as compared to the control. In group A, the HF-p increased after neostigmine but did not differ from the control. The difference between groups D and B was not statistically significant. From the results of this study, we concluded that the muscarinic effect of neostigmine could not be sufficiently blocked by atropine at 1/2 dosages of neostigmine, but could be sufficiently blocked by atropine at equivalent dosages of neostigmine, under light isoflurane anesthesia.

Key words: Heart rate spectral analysis, Reversal of residual neuromuscular blockade, Parasympathetic nervous system, Atropine, Neostigmine

Introduction

Neostigmine is administered for the reversal of residual neuromuscular blockade during anesthesia, and atropine is used to antagonize the muscarinic effects. However, the use of these two agents sometimes results in bradycardia, which is caused by an increase in parasympathetic activity and a decrease in sympathetic activity. Many investigators have studied the influence of atropine and neostigmine on heart rates and recovery from neuromuscular blockade in anesthetized patients [1-6]. However, each study has recommended different ratios of atropine and neostigmine doses (1:1-0.3:2.5), and there is no consensus about the ideal doses of atropine and neostigmine [1-6]. Moreover, Naguib and Gomaa suggested that in order to prevent late reductions in heart rates, the appropriate dose of atropine, when used with neostigmine, should be larger than that commonly used [1].

Recently, heart rate spectral analysis has become recognized as a powerful tool for quantitatively evaluating parasympathetic and sympathetic activity separately in awake and anesthetized humans [7-11]. It has been reported that the low-frequency component (LF-p) is mediated jointly by the sympathetic and parasympathetic nervous systems, whereas the high-frequency component (HF-p) is selectively mediated by the parasympathetic nervous system [7-11]. The purpose of this study was to assess parasympathetic nervous activity after administration of both atropine and neostigmine using heart rate spectral analysis.

Address correspondence to: K. Iwasaki
Received for publication on January 18, 1995; accepted on August 5, 1996
Methods

Approval of the Ethics Committee at Surugadai Nihon University Hospital was obtained. Informed consent for the study was obtained from 36 female patients (26–37 years of age), ASA PS I, who were scheduled for laparoscopic examination. All patients were premedicated with hydroxyzine 50 mg i.m. 45 min before the induction of anesthesia. On arrival to the operating room, ECG leads, pulse oximetry, and intravenous cannule were placed. Anesthesia was induced with thiamylal 5 mg·kg⁻¹, and suxamethonium 1 mg·kg⁻¹ was given to facilitate orotracheal intubation. Anesthesia was maintained with 1%–2% isoflurane and 70% nitrous oxide in oxygen, with intermittent administration of vecuronium bromide 0.08 mg·kg⁻¹. Breathing of the patients was controlled mechanically with 10–12 ml·kg⁻¹ tidal volume and 10 breaths·min⁻¹ (0.17 Hz) to maintain end-tidal carbon dioxide pressure (ETCO₂) at between 30 and 40 mmHg. After finishing the laparoscopic examination, additional anesthesia was maintained with 70% nitrous oxide, 30% oxygen, and 0.5% isoflurane. Within 10 min, the end-tidal isoflurane concentration had stabilized at 0.5%, and the patients’ heart rates had stabilized at the fasting level (62–89 min⁻¹).

The electrocardiogram (ECG), obtained from the third lead of a standard ECG instrument, was analyzed with an R-R analyzer (TM-55, Cerx, Tokyo, Japan) which allows direct computation of the R-R interval (ms). The analyzed R-R intervals (beat-to-beat mode) were sent to a microcomputer PC9801N (NEC, Tokyo, Japan) through an RS-232C line and were recorded on floppy disks. The mean heart rates (m-HR) were calculated from mean R-R intervals during 128 s. The R-R intervals (beat-to-beat mode) were changed to a time series data of 256 points every half second by the Spline interpolation method. Spectrum of R-R intervals were obtained by applying the fast Fourier transform (FFT) to the time series data and the Hanning window processing [12]. Power spectral density of the high-frequency component (HF-p) and low-frequency component (LF-p) were used to assess sympathetic and parasympathetic activity. In this study, we selected HF-p as an index to assess parasympathetic activity. The high-frequency component was centered at the frequency of respiration. We fixed the respiration rate at 10·min⁻¹ (0.17 Hz), and as a result the high-frequency component had a peak at 0.17 Hz. Therefore, we defined high frequency as 0.14–0.25 Hz and low frequency as 0.04–0.14 Hz.

The 36 patients were randomly allocated to one of the following four groups: In group A (1:1), atropine 1.0 mg (16–20 µg·kg⁻¹) was followed 4 min later by neostigmine 1.0 mg (16–20 µg·kg⁻¹) (9 patients). In group B (1:2), atropine 0.5 mg (9–11 µg·kg⁻¹) was followed 4 min later by neostigmine 1.0 mg (18–22 µg·kg⁻¹) (9 patients). In group C (1:2.5), atropine 1.0 mg (18–21 µg·kg⁻¹) was followed 4 min later by neostigmine 2.5 mg (45–53 µg·kg⁻¹) (9 patients). In group D (1:2 mix), a mixed solution of atropine 0.5 mg (9–10 µg·kg⁻¹) and neostigmine 1.0 mg (18–22 µg·kg⁻¹) was injected (9 patients). Each drug was injected intravenously over a period of 30 s.

The R-R intervals data were measured for 128 s from the ECG, before administration of atropine or the mixed solution of atropine and neostigmine as controls, between 2 and 4 min after administration of atropine, and between 5 and 7 min after administration of neostigmine.

In all group C patients, additional atropine was administrated 6 min after the neostigmine administration because of extreme bradycardia (HR ≤ 52), and data during 5–7 min following neostigmine administration could not be obtained in this group. Therefore, we used the data during 3–5 min following neostigmine administration instead. In group D, the R-R intervals data were obtained between 5 and 7 min after administration of the mixed solution.

Statistical analysis of the data was performed with the Friedman test in groups A, B, and C. Significance of difference was calculated using Dunnett’s test (two-tailed; P < 0.01 vs control). The difference between groups was evaluated by the unpaired Wilcoxon test (two-tailed; P < 0.01) on mean percent changes.

Results

The background data on physical status in the four groups were not significantly different. (Table 1). There were no ectopic beats and no other artefacts on the ECG. Spectra of R-R intervals such as those shown in Fig. 1 were obtained.

The mean values of each index in the four groups are summarized in Table 2. HF-p decreased significantly (P < 0.01) after atropine administration in groups A, B, and C. The HF-p increased after administration of neostigmine as compared to the control levels in groups B and C (P < 0.01), while no significant difference could be found in group A (Table 2). Percent changes in HF-p are presented in Fig. 2. After neostigmine administration, there was a significant difference both between groups A and B, and between groups A and C (P < 0.01).

LF-p decreased significantly (P < 0.01) after atropine administration in groups A, B, and C. The LF-p increased after administration of neostigmine as compared to the control levels in groups B and C (P < 0.01), while no significant difference could be found in group A (Table 2).