Antagonism of sevoflurane anaesthesia by physostigmine: effects on the auditory steady-state response and bispectral index

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Background. Physostigmine, a centrally acting anticholinesterase, antagonizes the hypnotic effect of propofol, as shown by the return of consciousness (response to commands) or wakefulness (spontaneous eye-opening without response to commands) and by recovery of auditory evoked potentials (40 Hz auditory steady-state response (ASSR)) and the bispectral index (BIS). We measured the effects of physostigmine on the hypnotic effect of inhaled volatile anaesthetics, using sevoflurane as the representative agent.

Methods. Eight healthy volunteers received sevoflurane adjusted to produce loss of consciousness. Physostigmine (plus glycopyrrolate) was given while the end-tidal concentration of sevoflurane was kept constant.

Results. Loss of consciousness was accompanied by a significant (P<0.02) decrease in ASSR amplitude (to 21% of awake value) and BIS (to 70% of awake value). Five subjects had return of consciousness or wakefulness after physostigmine. The others showed no behavioural change. Physostigmine caused a significant increase of the mean ASSR amplitude from 0.11 (SD 0.04) to 0.17 (0.06) µV (P<0.05). The BIS also increased, from 66 (12) to 74 (12), but the difference was not significant.

Conclusions. Physostigmine can antagonize, at least partially, the hypnotic effect of sevoflurane and changes in arousal after physostigmine are shown by ASSR measurements. However, the antagonism is not as clear or reliable as with propofol.

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Both nicotinic and muscarinic receptors are sensitive to general anaesthetics. While the role of central cholinergic transmission in clinical anaesthesia is not clear,1 2 drugs that affect central cholinergic activity can influence the anaesthetic effect. We have shown3 that increasing central cholinergic tone with the anticholinesterase physostigmine antagonizes the hypnotic effect of propofol, shown by the return of consciousness (defined as responsiveness to commands) or wakefulness (appearance of being awake with open eyes but without cognitive content, such as the ability to follow commands4) and by increases in the amplitude of the auditory steady-state response (ASSR) and in the bispectral index (BIS). We assessed the effects of physostigmine on the hypnotic effect of an inhaled volatile anaesthetic. We chose sevoflurane because it produces negligible irritation of the airway and is thus well suited for induction of anaesthesia.

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Methods and results

Subjects

After local ethical approval, 10 paid, fasting volunteers (ASA physical status I; 18–35 yr, mean 24 (sd 6) yr; two men) were tested. Subjects gave written consent and had a complete medical evaluation.

Anaesthesia, monitoring and drug administration

Subjects were given sodium citrate 30 ml orally. A cannula was inserted in a forearm vein. Monitoring included ECG, non-invasive blood pressure (right calf), pulse oximetry and respiratory gas analysis (oxygen, carbon dioxide and sevoﬂurane) with a Capnomac Ultima™ (Datex-Ohmeda, Helsinki, Finland) calibrated before use. Ondansetron 4 mg i.v. was given to reduce the risk of nausea and vomiting. The subjects breathed oxygen via a circle system connected to a tight-ﬁtting face mask. After obtaining baseline (BASE) measurements (recording of the ASSR, BIS and level of consciousness every 2 min for 20 min), sevoﬂurane was given to obtain an end-tidal concentration of 0.3%. The concentration was thereafter increased by 0.1% every 10 min until the subject became unconscious. This end-tidal concentration was kept constant for 15 min before recording measurements during unconsciousness (SEVO). While keeping the end-tidal concentration constant, an injection of physostigmine (28 μg kg⁻¹) plus glycopyrrolate (4.2 μg kg⁻¹) (PHYSO) or an equivalent volume of normal saline (NS) was given i.v. in a randomized, double-blind manner. Measurements were obtained starting 6 min after the injection (PHYSO or NS). A second injection (containing the substance not given in the first injection) was to be given 30 min after the first. However, the second injection was given only to subjects who had received NS first. Most subjects who had already received physostigmine and glycopyrrolate experienced nausea (six subjects, three of whom progressed to retching or vomiting), which required the cessation of sevoﬂurane administration. Measurements were made 30 min after stopping sevoﬂurane (RECOVERY) in those subjects who had no, or only mild, nausea (n=5).

ASSR, BIS and level of consciousness

The ASSR, BIS and level of consciousness were recorded every 2 min with the following schedule: 45 s for ASSR, 10 s for assessing the level of consciousness, 60 s without auditory stimuli, BIS reading, 45 s for ASSR, and so on. The level of consciousness was assessed using simple verbal commands (‘open your eyes’, ‘move your hand’) repeated up to three times with increasing forcefulness if the subject failed to respond.

The stimuli for the ASSR were 500 Hz tone-bursts (10 ms duration, 2 ms rise/fall, 82 dB peak equivalent sound pressure level) delivered at the rate of 40 s⁻¹ to both ears with insert earphones (EarTone 3A; Cabot, Indianapolis, IN, USA). The EEG was recorded from Cz with the right mastoid as reference using gold-cup electrodes filled with conductive gel (impedance <5 kΩ) and glued to the scalp with collodion-impregnated gauze. The vertical electro-oculogram was also recorded to help detect epochs contaminated by eye movements. The signal was amplified (gain, 20 000) with a bandpass of 0.1–100 Hz (model 12A5 amplifier; Grass Instruments, Quincy, MA, USA). The epoch lasted 2550 ms and contained 1024 data points (analogue-to-digital conversion rate 401.6 Hz, 12-bit resolution). Epochs contaminated by artefacts (more than 10% of epoch exceeding ±100 μV) were rejected. The remaining epochs were averaged in groups of 15 to obtain an ASSR sub-average. For the BASE, SEVO and RECOVERY periods, 10 sub-averages were obtained (20 min). For the NS and PHYSO periods, 15 sub-averages were obtained (30 min).

The BIS was recorded from FP1 and FP2 with FPz reference using an A-1000 monitor (bandpass 1.0–30.0 Hz; Aspect Medical Systems, Natick, MA, USA; software version 3.12) and gold-cup electrodes. A common ground electrode at FCz was used for both the ASSR and BIS recordings.

Data reduction

The ASSR amplitude for each subject and period was determined as follows. For all periods except PHYSO, the ASSR waveform used for analysis was the time-domain average of all recordings obtained within the period. For the PHYSO period, the procedure depended on whether the subject had responded to physostigmine (as described in the Results section). If there was a response to physostigmine, the ASSR waveform used for analysis was the time-domain average of the recordings obtained after the return of consciousness or wakefulness. If there was no response, all recordings obtained during the period were averaged. For all periods, the amplitude of the ASSR was measured by fast Fourier transform of the average waveforms. The BIS values were selected in a similar manner and the arithmetic mean retained for analysis.

Statistics

Exploratory analysis revealed that some variables were not normally distributed (Kolmogorov–Smirnov statistic, with Lilliefors’ procedure). Because data transformation did not correct this problem, we opted for the non-parametric Wilcoxon signed rank test. The criterion for significance was P<0.05. The sample size was adequate (power 0.8) to detect at the P<0.05 level an effect of physostigmine on ASSR or BIS one-half smaller than that seen with propofol.
Results

Two patients became agitated on loss of consciousness and required anaesthesia with sevoflurane 1.4 and 1.9%. Physostigmine was given with no effect on consciousness. These subjects were excluded from analysis.

Unconsciousness occurred at a mean (SD) sevoflurane concentration of 0.85 (0.18)%. The ASSR was reduced by sevoflurane from 0.51 (0.18) μV during baseline to 0.11 (0.04) μV during unconsciousness (P<0.05). The BIS was also reduced by sevoflurane from 95 (7) during baseline to 66 (12) during unconsciousness (P<0.05). After physostigmine, two subjects regained consciousness (response to commands) and three subjects regained wakefulness (they spontaneously opened their eyes but did not follow commands). The remaining three subjects kept their eyes closed and did not follow commands. Physostigmine caused a significant (P<0.05) increase in the ASSR amplitude to 0.17 (0.06) μV (Fig. 1). The BIS increased to 74 (12) but the difference was not significant (P=0.16). After NS, all four subjects remained unconscious and there were no changes in ASSR or BIS.

Comment

The present results show that physostigmine can antagonize the hypnotic effect of sevoflurane and that this is accompanied by a modest (although significant) increase in the amplitude of the ASSR, and to a lesser extent, of BIS. The antagonism of sevoflurane anaesthesia by physostigmine is, however, not as reliable as seen with propofol in our previous study.3 In that study, nine of 11 subjects regained consciousness, one regained only wakefulness and one remained unresponsive (91% response rate). These behavioural changes were accompanied by a marked increase in the ASSR and BIS.

Why is the hypnotic effect of sevoflurane less able to be antagonized by physostigmine than by propofol?3 The difference is not a result of CNS depression being greater during unconsciousness with sevoflurane. First, the ASSR during unconsciousness was similar for the two drugs (0.11 (0.04) μV with sevoflurane and 0.10 (0.08) μV with propofol), suggesting a similar degree of depression. Secondly, BIS during unconsciousness with sevoflurane was higher (66 (12)) than with propofol (56 (9)) (P<0.005; Mann–Whitney U test with present results and data from our propofol study), perhaps suggesting less CNS depression with sevoflurane. The finding of a higher BIS value during sevoflurane-induced unconsciousness is consistent with previous observations7 and may explain why the increase in BIS after physostigmine did not reach significance.

The present findings are surprising in view of recent observations by Paraskeva and colleagues.8 These authors observed no behavioural or BIS change after giving physostigmine during sevoflurane anaesthesia. The concentration of sevoflurane (0.60% vol end-tidal) was lower than ours (0.85% vol). Several factors may account for the discrepancy between the two studies. Paraskeva and colleagues studied surgical patients whereas we studied volunteers not undergoing surgery. The surgical patients were exposed to a higher concentration of sevoflurane and to noxious stimulation (tracheal intubation, surgical incision) before the study and they were paralysed with rocuronium during the study. They also received metoclopramide and droperidol for antiemetic prophylaxis; our subjects were given ondansetron. In contrast to the study of Paraskeva and colleagues, Hill and colleagues9 reported that physostigmine decreased the time for return of consciousness after halothane anaesthesia, suggesting that reversal does occur.

The frequency of nausea after physostigmine interfered with our attempt to conduct the study in a blinded manner. While we cannot rule out a bias in the assessment of the level of consciousness with absolute certainty, we feel that this is unlikely to have exerted a major influence on the outcome of the study.

Fig 1 (A and C) Individual ASSR and BIS data for the Sevo and Physo periods. Each line represents one subject. The three subjects who showed no behavioural response to physostigmine are represented by filled symbols. (B) ASSR amplitude and BIS (n=8) [mean (SD)]. Base=awake baseline; Sevo=unconsciousness induced by sevoflurane; Physo=after physostigmine while keeping sevoflurane at same concentration; Reco=recovery (n=5). *Less than Base and Reco for both ASSR and BIS (P<0.05); †higher than Sevo for ASSR (P<0.05); ‡less than Base for both ASSR and BIS (P<0.05).
The robust association between profound attenuation of ASSR and unconsciousness caused by general anaesthetics suggests that anaesthetic-induced unconsciousness is associated with a reduction of gamma or 40 Hz oscillations in thalamocortical systems. These rhythms constitute background activity reflecting depolarization of thalamic and cortical neurons, a physiological condition required for consciousness. An interesting possibility is that antagonism of anaesthetic effect by physostigmine would result from potentiation of 40 Hz oscillations via increased muscarinic tone. The ASSR data suggest that potentiation of gamma oscillations by physostigmine during sevoflurane anaesthesia is not as strong as with propofol.

We conclude that physostigmine can, at least partially, antagonize the hypnotic effect of sevoflurane and that the resulting arousal is reflected by an increase in the amplitude of the ASSR and, to a lesser extent, of BIS. The effect is not as clear or reliable as that seen with propofol.

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