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Antagonism of neuromuscular blockade but not muscle relaxation affects depth of anaesthesia

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Background. Conflicting effects of neuromuscular blocking drugs and anticholinesterases on depth of anaesthesia have been reported. Therefore we evaluated the effect of atracurium and neostigmine on bispectral index (BIS) and middle-latency auditory evoked potentials (AAI).

Methods. We studied 40 patients (ASA I–II) aged 18–69 yr. General anaesthesia consisted of propofol and remifentanil by target-controlled infusion and neuromuscular function was monitored by electromyography. When BIS reached stable values, patients were randomly assigned to one of two groups. Group 1 received atracurium 0.4 mg kg^{-1} and, 5 min later, the same volume of NaCl 0.9%; group 2 received saline first and then atracurium. When the first twitch of a train of four reached 10% of control intensity, patients were again randomized: one group (N) received neostigmine 0.04 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1}, and the control group (G) received only glycopyrrolate.

Results. Injection of atracurium or NaCl 0.9% had no effect on BIS or AAI. After neostigmine–glycopyrrolate, BIS and AAI increased significantly (mean maximal change of BIS 7.1 [SD 7.5], $P<0.001$; mean maximal change of AAI 9.7 [10.5], $P<0.001$). When glycopyrrolate was injected alone BIS and AAI also increased (mean maximal change of BIS 2.2 [3.4], $P=0.008$; mean maximal change of AAI 3.5 [5.7], $P=0.012$), but this increase was significantly less than in group N ($P=0.012$ for BIS; $P=0.027$ for AAI).

Conclusion. These data suggest that neostigmine alters the state of propofol–remifentanil anaesthesia and may enhance recovery.

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Clinically, it has been suspected that reversing neuromuscular block by injection of an anticholinesterase agent may induce arousal and even awareness.[1 2] On the other hand, injection of a neuromuscular blocking drug appears to deepen the level of anaesthesia.[3] Meuret and colleagues[2] have reported reversal of propofol-induced unconsciousness by physostigmine, an anticholinesterase that crosses the blood–brain barrier. This is probably a result of altered central cholinergic transmission. Indeed, it is postulated that inhibition of central cholinergic transmission may play an important role in the mechanism by which general anaesthetic drugs produce unconsciousness.[2 4 5] Physostigmine has also been shown to increase the amount of propofol required to induce loss of consciousness.[1]

Neostigmine, which is the anticholinesterase agent commonly used in clinical practice, does not cross the blood–brain barrier.[6] Therefore the central mechanism by which physostigmine may induce arousal is not applicable to neostigmine. The afferentation theory states that signals from muscle stretch receptors (proprioception) stimulate arousal centres in the brain.[7] This theory has, in part, been confirmed by some studies: neuromuscular block has been reported to reduce the minimum alveolar concentration (MAC) by 25%,[3] and active muscle movement in lightly anaesthetized dogs had an activating effect on the electroencephalogram, whereas paralysis with pancuronium abolished movement-induced stimulation.[7] However, other studies have failed to confirm these findings,[8 9] and no study so far has investigated the effect of neostigmine on the depth of anaesthesia as assessed by bispectral index (BIS).

Therefore the aim of this study was to evaluate the variation in the depth of anaesthesia during propofol–remifentanil anaesthesia, as assessed by BIS and middle-latency auditory evoked potentials (A-Line® autoregressive index [AAI]) induced by either muscle relaxation or antagonization of neuromuscular blockade.

Methods

After institutional ethics committee approval and written informed consent, 40 patients aged 18–69 yr, ASA status I or II, scheduled for elective surgery requiring general anaesthesia and intubation were included in this prospective randomized double-blinded study. Patients were excluded if they had cardiopulmonary, renal, hepatic or neurological disorders, if they had a history of chronic alcohol consumption and/or drug abuse, and if they were taking any medication affecting neurological or neuromuscular function.

Experimental protocol

No premedication was given. Target effect site concentration was used for induction and maintenance of general anaesthesia. The pharmacokinetic sets used to calculate target effect site concentrations of propofol and remifentanil were those published by Minto and colleagues[10] and Schnider and colleagues,[11] respectively. Remifentanil was kept at 3 ng ml^{-1} and propofol was raised in incremental steps until unconsciousness, defined by loss of verbal contact. For intubation, target effect site concentration was increased to 6 ng ml^{-1} for remifentanil and to 6 μg ml^{-1} for propofol. Tracheal intubation was performed without the use of neuromuscular blocking drugs.[12,13] The lungs were mechanically ventilated with 50% oxygen in air to maintain end-tidal P_{CO_2} between 4.4 and 5.1 kPa. Hypotension was treated first with 500 ml Ringers solution and then with ephedrine 5 mg i.v.

Non-invasive blood pressure, heart rate, peripheral arterial oxygen saturation and end-tidal P_{CO_2} were recorded at 1-min intervals. Core temperature was measured using an oesophageal thermometer (AS3® monitor, DATEX, Helsinki, Finland). Neuromuscular function was monitored by electromyography (EMG) with repeated train-of-four (TOF) sequences applied via surface electrodes to the ulnar nerve at the wrist. TOF was repeated every 20 s. The resulting integrated EMG of the adductor pollicis muscle was measured (ElectroSensor type M-NMT.02, DATEX, Helsinki, Finland) to monitor muscle relaxation and recovery. The hand was fixed to guarantee immobility and stable responses. The first TOF sequence served as the control reference with which all subsequent first twitches were compared (T1%). EMG and mechanomyography are comparably reliable in patients without neuromuscular diseases,[14] but EMG is easier to use. We were interested in a specific predetermined endpoint (first twitch in TOF as 10% of preblock value).

The level of consciousness was assessed by BIS and AAI. The forehead was cleaned with ether and then abraded with gauze. BIS electrodes (Zipprep™ electrodes, Aspect Medical Systems) and AAI electrodes (A-Line® auditory evoked potential electrodes; Danmeter A/S, Odense, Denmark) were positioned according to the manufacturer's recommendation on forehead, temple and mastoid. Depth of anaesthesia, as assessed by BIS (A-2000™ BIS™ XP Monitor, software version 3.4, Aspect Medical Systems Inc., Newton, MA, USA) and AAI (A-Line Monitor, Danmeter A/S, Odense, Denmark), and frontotemporal EMG power (expressed in decibels with respect to 0.0001 μV^2) at 70–110 Hz (Aspect Medical Systems A-2000™ BIS™ Monitor) were recorded continuously. The middle-latency auditory evoked potentials (MLAEP) were elicited with a bilateral click stimulus of intensity 70 dB and duration 2 ms.

After intubation, remifentanil target effect site concentration was decreased to 3 ng ml^{-1} and the propofol target was adjusted in steps of 0.1–0.5 μg ml^{-1} to achieve a steady-state level of anaesthesia for at least 5 min at a BIS of 55 (2). The A-2000™ BIS™ XP Monitor always recorded EMG simultaneously with BIS.

In the first part of the study, patients were randomly assigned to one of two groups (n=20 each). A nurse not involved in the study prepared the study drugs based on the randomization list. The drugs were blinded for the investigators. Group 1 received atracurium 0.4 mg kg^{-1} and 5 min later the same volume of NaCl 0.9%. Group 2 received these drugs in reverse order (saline, then atracurium). After this part of the study, anaesthesia was again maintained at stable BIS values until the first twitch of a TOF reached 10% of control value.[15]

In the second part of the study, patients were again randomly assigned to one of two groups. One group (N) received neostigmine 0.04 mg kg^{-1} and glycopyrrolate 0.01 mg kg^{-1}; the control group (G) received only glycopyrrolate 0.01 mg kg^{-1}. The first and second randomizations were completely independent. Glycopyrrolate was administered together with neostigmine to block the peripheral muscarinic side-effects of neostigmine. Patients were kept normothermic by increasing room temperature. No surgery was performed during the study. After completion of the study, anaesthesia was continued with propofol and fentanyl and surgery was performed as planned. All patients were interviewed after the operation in the recovery room and on the ward.

The propofol target effect site concentration was noted at the moment of injection of atracurium or saline in the first part of the study and neostigmine and/or glycopyrrolate in the second part.

Data analysis

For each patient, baseline values for BIS, AAI and EMG were averaged over 1 min before injection of the assigned study drug. Subsequently, after the injection of the neuromuscular blocking drug, the anticholinesterase or the control, values were averaged every minute for 5 min in the first part of the study and for 10 min in the second part. Criteria for termination of the recordings following neostigmine–glycopyrrolate or glycopyrrolate were a T1% of 60% of control value or if the patient showed clinical signs of arousal such as coughing or opening the eyes.

The maximal change of BIS and AAI for each group was compared with the baseline values and between groups. EMG at the time of maximal change of BIS was compared with baseline values.

Statistical analysis

Statistical analysis was performed with using JMP software (JMP version 5.0.1a, SAS Institute Inc., Cary, NC, USA). The estimated sample size in each group was based on the study by Meuret and colleagues.[2] Accepting a type I error of 5% and a type II error of 20%, we calculated that the number of patients necessary was n=15.6. Therefore we studied two groups of n=20 each.

The physical characteristics between groups were compared using Student's t-test. Baseline BIS and AAI values and the mean maximal change of BIS and AAI were compared with a two-way ANOVA for repeated measurements on one way (time), followed by paired and unpaired Student's t-tests with Bonferroni's correction.

Results are expressed as mean (SD). The criterion for statistical significance was P<0.05.

Table 1 Patient characteristics. Values are mean (range), mean (SD) or absolute count. Group 1, atracurium then NaCl 0.9%; group 2, NaCl 0.9% then atracurium; group N, neostigmine–glycopyrrolate; group G, glycopyrrolate. NS, not significant

	Group 1	Group 2	*P*-value	Group N	Group G	*P*-value
Age (yr)	40 (19–63)	39 (18–69)	NS	40 (19–69)	39 (18–61)	NS
Gender (F/M)	7/13	6/14	NS	6/14	7/13	NS
BMI (kg m^{-2})	23 (3)	23 (3)	NS	23 (3)	24 (3)	NS
ASA I/II	15/5	12/8	NS	14/6	13/7	NS
Smoker (yes/no)	7/13	7/13	NS	6/14	8/12	NS

Table 2 Baseline (1 min before injection of the study drug) values for BIS and AAI. Group 1, atracurium then NaCl 0.9%; group 2, NaCl 0.9% then atracurium; group N, neostigmine–glycopyrrolate; group G, glycopyrrolate. Baseline values were averaged over 1 min before injection of the assigned study drug. Normal sleep ranges for BIS, 40–60; normal sleep ranges for AAI, 20–40. NS, not significant

	Group 1	Group 2	*P*-value	Group N	Group G	*P*-value
AAI	27 (13)	23 (6)	NS	23 (7)	23 (8)	NS
BIS	56 (6)	56 (6)	NS	54 (6)	56 (6)	NS

Results

The groups were similar regarding patient characteristics (Table 1). Only two patients needed ephedrine 5 mg to treat hypotension, which was administered in the phase between the two parts of the study. There was no difference between the groups at baseline for BIS or AAI (Table 2). There was also no difference in the baseline values between the two parts of the study. After injection of atracurium or NaCl, no decrease was seen for BIS (mean maximal change after injection of atracurium, −0.6 [4.7], NS; after NaCl 0.9%, 2.0 [4.1], NS; or AAI (mean maximal change after injection of atracurium, −1.4 [12.5], NS; after NaCl 0.9%, 5.8 [12.1], NS).

In the second part of the study, the mean maximal increase of BIS and AAI after injection of neostigmine–glycopyrrolate was significant compared with baseline (BIS, 7.1 [7.5], P<0.001; AAI, 9.7 [10.5], P<0.001). When glycopyrrolate was injected alone we also noted an increase of BIS and AAI (BIS, 2.2 [3.4], P=0.008; AAI, 3.5 [5.7], P=0.012), but this increase was significantly less than that with neostigmine–glycopyrrolate (BIS P=0.012, AAI P=0.027) (Fig. 1). Three patients showed unexpected movements and coughing after injection of neostigmine. One patient remembered this episode.

At baseline and during the first part of the study there was no difference between the two groups with regard to haemodynamic values. After injection of glycopyrrolate alone, mean arterial pressure and heart rate increased significantly and were significantly higher than in the neostigmine–glycopyrrolate group (Table 3).

The values of the EMG recorded by the BIS electrode at the moment of the maximal change of BIS are shown in Table 4. There was a significant decrease in EMG after the injection of atracurium in groups 1 and 2. In the second part of the study there was a significant increase in EMG after the injection of neostigmine–glycopyrrolate.

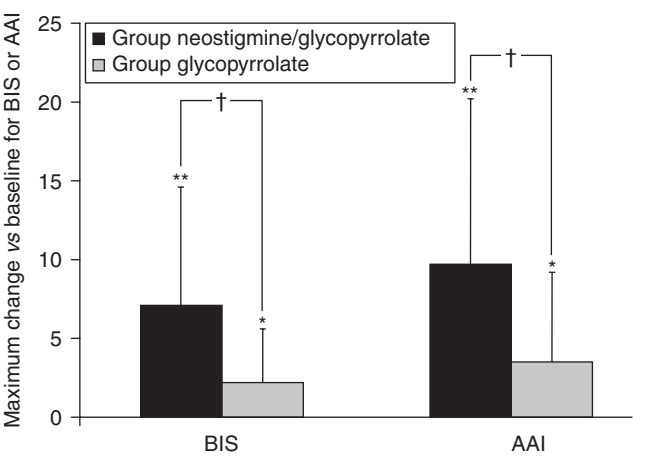

Fig 1 Mean maximal change and standard deviation of BIS and AAI after the injection of either neostigmine–glycopyrrolate or glycopyrrolate alone (control). BIS and AAI increase significantly in both groups, but this increase is significantly less in the glycopyrrolate group than when neostigmine and glycopyrrolate are injected. *P<0.05, **P<0.01 for maximum change *vs* baseline; †P<0.05 between groups.

The target effect site of propofol used to maintain BIS at 55 did not vary significantly throughout the study (baseline part 1, 2.1 [0.5] μg ml^{-1} *vs* baseline part 2, 2.0 [0.5] μg ml^{-1}, NS) or between groups in the first and second parts of the study (part 1: group 1, 2.1 [0.6] μg ml^{-1} *vs* group 2, 2.0 [0.5] μg ml^{-1}, NS; part 2: group N, 2.1 [0.5] μg ml^{-1} *vs* group G, 2.0 [0.5] μg ml^{-1}, NS).

Table 3 Heart rate (HR) and mean arterial pressure (MAP). HR baseline, HR before injection; HR max, HR at time of maximal change of BIS; MAP baseline, MAP before injection; MAP max, MAP at time of maximal change of BIS; NS, not significant

	HR baseline (beats min^{-1})	HR max (beats min^{-1})	MAP baseline (mm Hg)	MAP max (mm Hg)
Group 1: first atracurium	60 (12)	60 (12)	70 (11)	70 (12)
Group 2: first NaCl	63 (9)	63 (8)	73 (5)	74 (9)
P-value	NS	NS	NS	NS
Group 1: NaCl (5 min later)	59 (10)	59 (10)	70 (11)	70 (10)
Group 2: atracurium (5 min later)	63 (7)	63 (8)	74 (9)	72 (7)
P-value	NS	NS	NS	NS
Group N: neostigmine–glycopyrrolate	59 (9)	60 (10)	71 (10)	75 (13)
Group G: glycopyrrolate	60 (10)	77 (9)	74 (7)	85 (8)
P-value	NS	<0.0001	NS	0.01

Table 4 EMG (dB) before and after injection. EMG baseline, EMG values before injection; EMG max, EMG at time of maximal change of BIS; NS, not significant

	EMG baseline (dB)	EMG max (dB)	*P*-value
Part 1			
Group 1: first atracurium	29.7 (2.4)	28.2 (1.6)	0.006
Group 2: first NaCl	31.0 (3.1)	32.0 (4.5)	NS
Group 1: NaCl (5 min later)	28.3 (1.6)	28.1 (1.6)	NS
Group 2: atracurium (5 min later)	30.5 (2.5)	28.6 (1.5)	0.039
Part 2			
Group N: neostigmine–glycopyrrolate	27.7 (1.3)	31.2 (5.3)	0.006
Group G: glycopyrrolate	29.1 (3.2)	29.7 (3.8)	NS

Discussion

This study shows that the anticholinesterase neostigmine alters the depth of propofol anaesthesia and enhances recovery, as assessed by BIS and AAI measurements. Moreover, three patients showed unexpected movements and coughing after injection of neostigmine, suggesting that it had an arousal effect. One patient even remembered this episode. In contrast, muscle relaxation had no effect on the depth of anaesthesia.

This finding may have some clinical relevance. Indeed, despite an adequate level of anaesthesia (BIS 40–60), unexpected patient movement during recovery of anaesthesia at the end of operation may interfere with surgery or dressing. Moreover, alteration of the level of anaesthesia may lead to awareness and recall. The anaesthetic effect of neuromuscular blocking drugs has been discussed for many years and clinical data are still conflicting. In 1997, Forbes and colleagues[3] found that pancuronium reduces halothane requirements in humans. One possible explanation could be the afferent muscle spindle theory, which was developed in the 1960s and expanded by Lanier and colleagues[7] to explain their finding that paralysis by pancuronium diminishes EEG activity in dogs. Neuromuscular blocking drugs may alter cerebrocortical activity by changing proprioceptive afferent activity from muscles. The afferent muscle spindle theory predicts that agents or manoeuvres that actively or passively cause muscle stretch or contraction will stimulate the arousal centres in the brain. Consistent with this theory, Schwartz and colleagues[16] found that pancuronium increases the duration of electroencephalogram burst suppression in dogs anaesthetized with isoflurane. This increase was reversed by neostigmine. Our study also supports this theory; increases in muscle afferent activity by antagonizing the neuromuscular block result in a sustained cerebral arousal response during propofol–remifentanil anaesthesia.

In keeping with the afferentation theory, if a muscle relaxant is injected, deafferentation will occur which should deepen the level of anaesthesia. In a study of paralysed dogs, the cerebral response to noxious stimulation during light halothane anaesthesia was attenuated compared with non-paralysed dogs.[7] It has recently been shown in intensive care patients receiving light sedation (BIS 65–80) that muscle relaxation deepens the level of anaesthesia as assessed by BIS monitoring.[17]

However, Lanier and colleagues could not demonstrate any effect of muscle relaxation or antagonism on anaesthetic depth. The combination of neostigmine and glycopyrrolate produced no changes in EEG, cerebral blood flow, cerebral metabolic rate for oxygen or intracranial pressure in dogs anaesthetized with halothane. These authors concluded that neostigmine–glycopyrrolate had no specific cerebral effect on paralysed dogs.

It is possible that afferentation has only a weak central effect. Therefore, at deep levels of anaesthesia, this effect is too small to measurably affect the level of anaesthesia. On the other hand, during light anaesthesia, this effect may be enough to induce arousal. Greif and colleagues[9] examined the effect of muscle relaxation on BIS at different levels of neuromuscular blockade. They found no alteration in hypnotic level after the administration of mivacurium. The baseline BIS level before the injection of the neuromuscular blocking drug was 40 (5), corresponding to a deep hypnotic state.

The absence of an effect of atracurium on BIS and AAI in our study is not due to a different depth of anaesthesia, as baseline values for BIS and AAI before each part of the

study were not different (Table 2). This may be related to the fact that various muscle groups have various time courses of muscle relaxation and therefore the disappearance of the proprioception signal will occur slowly.[19 20] On the other hand, neostigmine may induce recovery of nearly all muscle activity simultaneously and this may stimulate a rapid increase in the proprioception signal.

We also measured a slight arousal effect when glycopyrrolate alone was given. This increase in BIS and AAI measurements could be explained by spontaneous recovery of muscle function after atracurium by a similar mechanism to the combined neostigmine–glycopyrrolate injection. However, the increase after neostigmine–glycopyrrolate was significantly more than with glycopyrrolate alone.

A major limitation of this study is the possible interference of EMG activity which has been reported to increase BIS.[17 21 22] Although the potential measured by BIS is predominantly EEG, potentials from other sources like muscular activity or electrode motion may compromise the measured signal. Appropriate filtering attenuates these artifacts. As the spectral power of the scalp EEG signal has a small amplitude at relatively high frequencies, interpretation of the EEG signal could be confounded with significant frontal electromyographic EMG spectral power. Since EEG and EMG artifacts overlap in the 30–50 Hz ranges, simple filtering will not completely remove the EMG artifact from single-channel EEG recordings. Substantial EEG power in the 30–50 Hz range is typically associated with awake or lightly sedated patients. EMG was continuously recorded throughout the procedure by the BIS electrodes. In the second part of the study the EMG values increased significantly after injection of neostigmine–glycopyrrolate, which was not the case when glycopyrrolate was injected alone. Nevertheless, this increase is unlikely to be responsible for the arousal effect demonstrated by BIS and AAI. Indeed, the variation in absolute EMG values is very small (27.7 [1.3] to 31.2 [5.3] dB after injection of neostigmine–glycopyrrolate, compared with 29.1 [3.2] to 29.7 [3.8] after glycopyrrolate alone), and there is no difference between the two groups. Moreover, in the first part of the study, injection of atracurium was associated with a significant decrease in the EMG, but without any effect on the BIS or AAI values. Therefore the arousal effect of neostigmine is unlikely to be primarily caused by an EMG artifact.

A second limitation of this study is the use of atracurium. The benzylisoquinoline derivative atracurium is a widely used non-depolarizing neuromuscular blocking agent which was chosen because of its relatively short half-life and its rapid elimination period.[23] It is unlikely that laudanosine or atracurium cause a clinical significant effect with the doses administrated in our study. Fahey and colleagues[24] could not demonstrate measurable concentrations ($\geqslant$2 ng ml^{-1}) of atracurium in cerebrospinal fluid after i.v. administration of atracurium 0.5 mg kg^{-1}.[24]

In conclusion, our data suggest that neostigmine alters the state of propofol–remifentanil anaesthesia and enhances recovery. The arousal effect recorded by BIS and AAI probably corresponds to a sudden increase in afferent signals from muscle stretch receptors.

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