British Journal of Anaesthesia **94 (6)**: 742–7 (2005)
doi:10.1093/bja/aei120 Advance Access publication March 18, 2005

BJA

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

F. C. Vasella, P. Frascarolo, D. R. Spahn and L. Magnusson*

Department of Anaesthesiology, University Hospital, CHUV BH-10, 1011 Lausanne, Switzerland
**Corresponding author: E-mail: Lennart.Magnusson@chuv.hospvd.ch*

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.

Br J Anaesth 2005; **94**: 742–7

Keywords: anaesthesia, depth; monitoring, bispectral index; muscle, relaxation

Accepted for publication: February 8, 2005

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.