Entropy of EEG during anaesthetic induction: a comparative study with propofol or nitrous oxide as sole agent

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Background. The search continues for an anaesthetic monitor that can define the level of anaesthesia in an individual patient irrespective of anaesthetic agent(s) used. Studies of available monitors based on bispectral analysis or evoked auditory potentials show the complexity of the problem. We assessed a new monitor, based on the entropy of the EEG, during induction of anaesthesia with either propofol or nitrous oxide.

Methods. In an open, randomized study (two groups; \( n = 10 \)) of day surgical patients, we induced loss of response with incremental boluses of propofol. The other group was given propofol 30 mg and then increasing concentrations of nitrous oxide until loss of response. We measured entropy with the M-Entropy Module S/5™ (Datex-Ohmeda) using forehead electrodes and recorded response entropy (RE; including frontal electromyogram) and state entropy (SE; only the cortical EEG). Values are median (range).

Results. Baseline values were RE 98 (96–100), SE 89 (87–91) and RE 98 (96–99), SE 89 (87–91) for the propofol and nitrous oxide patients, respectively. During propofol induction, both entropy indices decreased with increasing sedation, with RE 40 (23–76) and SE 34 (17–70) at loss of response. Neither RE nor SE decreased during nitrous oxide inhalation, and at loss of response using nitrous oxide, RE and SE were unchanged at 98 (96–100) and 88 (85–91) respectively.

Conclusions. The entropy monitor of anaesthetic depth shows a successive decrease with propofol but loss of consciousness with nitrous oxide is not associated with change in entropy indices.

Br J Anaesth 2004; 92: 167–70

Keywords: anaesthesia, depth; anaesthetics gases, nitrous oxide; anaesthetics i.v., propofol; complications, entropy; monitoring, EEG

Accepted for publication: August 27, 2003

Monitoring anaesthetic depth has proved to be unexpectedly difficult. The two monitors which are commercially available, the BIS monitor, providing the bispectral index (BIS), and the A-line monitor, providing the AAI™ index (calculated from the auditory evoked potential), have disturbingly large inter-individual variation, a lack of linearity in dose–response, and behaviour which differs for different anaesthetic agents.¹–³ While average values can be established for loss of response (LOR) and for threshold values to prevent awareness, the predictive value for the individual patient in the clinical setting is too low to guide the clinician dependably.

BIS calculates an index from the passively recorded EEG while the AAI™ index actively tests the EEG response to an auditory stimulus. Until recently these were the only commercially available anaesthetic depth monitors. An alternative approach for assessing loss of consciousness is to quantify the degree of spatial and temporal integration of cerebral neuronal activity using entropy principles. A loss of integrated neuronal activity, or increased entropy, has been related to the degree of consciousness during anaesthesia.⁴ For a monitor of anaesthetic depth to be useful in clinical

This article is accompanied by Editorial I.
practice, it should be insensitive to the type of anaesthetic agents used.

We compared the effects of propofol and nitrous oxide on EEG entropy during induction in day-surgery patients using a recently available monitor. The entropy index was determined until loss of response during induction with each of these agents.

**Patients and methods**

In an open, prospective randomized fashion, we studied 20 patients (five males, 15 females, age 23–70 years, 50–78 kg) having elective day surgery after informed consent and approval from the local ethics committee. We measured the entropy indices response entropy (RE) and state entropy (SE) during induction to loss of response to verbal command (LOR) using two induction techniques: the propofol group (n=10) received successive 30 mg doses of propofol every 2 min until LOR. The N₂O group (n=10) received premedication with propofol 30 mg i.v. After 5 min, nitrous oxide was given and slowly increased once every minute in increments of 10% to a maximal concentration of 75%. Measurements were made when the end-tidal nitrous oxide concentrations stabilized at each 10% increment.

A circle system with a fresh gas flow of 6 litres min⁻¹ was used and the patients breathed through a facemask held by a single investigator (JJ). Baseline measurements were made after resting 5 min in the supine position. Loss of consciousness was determined as loss of response to verbal commands. At the end of the study period (LOR), anaesthesia was deepened with an appropriate dose of propofol, a laryngeal mask airway was inserted, and surgical anaesthesia was achieved with sevoflurane.

**Monitor**

A special composite electrode with three elements was applied to the forehead in accordance with the manufacturer’s instruction and connected to the entropy monitor (M-Entropy plug-in Module S/5™; Datex-Ohmeda Division, Instrumentarium Corporation, Helsinki, Finland). After an initial control for electrode impedance, the monitor calculates an index from the raw EEG signals using an unpublished algorithm based on entropy principles. Initial sampling time is 30 s with updating every 10 s. The indices RE and SE were read manually (JJ) and recorded. The frontal electromyogram is included in the entropy analysis yielding RE, while only the cortical EEG is evaluated in the SE index.

Unconsciousness was defined during the transition from awake, still responding to loud verbal command, to LOR (loss of response to loud verbal commands by name and gentle shaking on the shoulder). During induction with nitrous oxide, only loss of response was recorded as the patients experienced a stage of excitation making more complex assessment impossible. During propofol induction, the Observer’s Assessment of Alertness/Sedation (OAAS) rating scale was used (score 5=awake and responds readily to name spoken in normal tone; 4=lethargic response to name in normal tone; 3=responds only after name is called loudly and/or repeatedly; 2=responds only after name called loudly and after mild shaking; 1=does not respond when name is called and mild shaking).

Other routine monitoring included single-channel ECG, pulse oximetry, end-tidal carbon dioxide and non-invasive systemic blood pressure.

**Statistics**

Results are presented as median (range). Entropy was shown to be normally distributed as indicated by histograms of the two variables, and therefore parametric statistics were used. The effect of increasing end-tidal concentrations of nitrous oxide and propofol on entropy was studied by repeated-measures ANOVA. P <0.05 was considered statistically significant.
Results

Baseline values without any propofol premedication (propofol group) were RE 98 (96–100) and SE 89 (87–91). Baseline values after propofol 30 mg premedication (nitrous oxide group) were RE 98 (96–99) and SE 89 (87–91).

Both RE and SE decreased gradually during propofol sedation, while no change in either RE or SE was noticed during inhalation of increasing concentrations of nitrous oxide (Figs 1 and 2). All patients reached loss of response to verbal command at a propofol dose of 180 mg or less than 2.5 mg kg\(^{-1}\), and all nitrous oxide patients reached loss of response to verbal command at or before 75% nitrous oxide. Slight excitement and an increased respiratory frequency was noted in most nitrous oxide patients at a concentration of 40–50%. RE at LOR was 40 (23–76) and 98 (96–100), SE 34 (17–70) and 88 (85–91) for propofol and nitrous oxide respectively. In the propofol group both RE and SE was significantly less at OAAS 1 and 2 vs OAAS 5 (P<0.01).

Discussion

We set out to compare the effect on EEG entropy of induction of loss of consciousness with propofol or nitrous oxide as a sole agent after a premedication dose of propofol 30 mg. We found that propofol caused a progressive decrease in both the RE and SE entropy indices, with markedly lower values at LOR. However, loss of consciousness, defined as loss of response to verbal command, with nitrous oxide did not change EEG entropy. It is important to consider that our observations were made during anaesthetic induction with a single agent and that no surgical stimulation was employed.

The goal for devices measuring depth of anaesthesia is to ascertain an adequate, but not excessive, depth of anaesthesia regardless of drug or drug combination used. Such devices should allow optimal delivery of drug or drugs to each patient, to guarantee an adequate depth of anaesthesia, loss of awareness and no recall.

Day surgery with propofol is an important clinical setting for monitors of anaesthetic depth, where minimizing drug use may aid rapid turnover. This study shows the same good correlation between propofol sedation and entropy indices as was recently shown by Bruhn using a non-commercial entropy monitor.\(^4\) We recorded both the response and the state entropy indices provided by the monitor, and found that although the values were slightly different they showed the same pattern during propofol as well as nitrous oxide induction. Earlier studies showed that BIS and the auditory evoked potential react to increasing levels of sedation with propofol.\(^5\)–\(^8\) From the present results we cannot tell whether entropy is more or less reliable than BIS or auditory evoked potential for determining the depth of anaesthesia. In a comparison of different neurophysiological techniques, Muncaster and colleagues found entropy processing of the EEG to be more sensitive than BIS and auditory evoked potential.\(^3\)

At 75% nitrous oxide all 10 patients did not react to verbal command but the entropy indices did not change. The mechanism of action of nitrous oxide is not completely understood but at least part of the effect is believed to be mediated through release of endogenous neuromediators. Release of both endorphin and norepinephrine is stimulated by nitrous oxide.\(^9\)–\(^10\) For a given level of sedation or hypnosis, the differences in EEG effects elicited by nitrous oxide and other potent anaesthetics may reflect differences.
in the mechanisms involved. The problem in detecting nitrous oxide effects by neurophysiological methods was shown in an earlier study in which loss of response to verbal command with end-tidal nitrous oxide concentrations up to 70% produced no change in BIS in any patient.\textsuperscript{11} Rampil and colleagues studied volunteers at concentrations up to 50% concentration of nitrous oxide and found little sedation and no change in BIS.\textsuperscript{12} They observed activation in certain spectral regions of the EEG not detected by the BIS algorithm and proposed that nitrous oxide possesses both excitatory and inhibitory CNS effects. Our findings support their hypothesis that nitrous oxide concentrations greater than 50% would lead to sedation/hypnosis, but the EEG changes they predicted were not substantiated by our findings. Other neurophysiological studies with nitrous oxide have shown varying effects of nitrous oxide, such as minor effects on auditory evoked potentials.\textsuperscript{13} The effects on mid-latency auditory evoked response have been shown to be less for nitrous oxide than for isoflurane in MAC equivalent concentrations.\textsuperscript{14,15} Nitrous oxide has, however, effects on the somato-evoked response, the N\textsubscript{2}O wave, which were more pronounced than that of isoflurane.\textsuperscript{15,16}

Limitations of this study include the lack of surgical stimulation. We intended to consider the elusive problem of determining the point of loss of response with hypnotics while the analgesia–pain relationship is often reflected by haemodynamic changes. Extrapolating from a sole-agent study to clinical practice, where several agents are used, must be done with care, but the present findings strongly suggest that using nitrous oxide together with other agents will increase hypnosis without any decrease in entropy indices.

We found that increasing levels of sedation provided by propofol during induction in a clinical setting change the entropy indices and that entropy at LOR is significantly different from fully awake values. Entropy indices are not altered when loss of response is achieved with nitrous oxide. Further studies are necessary to determine the role of EEG entropy monitoring in clinical practice when several anaesthetics interact and surgical stimuli are present.

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