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Original Article

Differential frontal alpha oscillations and mechanisms underlying loss of consciousness: a comparison between slow and fast propofol infusion rates

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[Correction added on 30 Dec 2019, after first online publication: The author, L. I. Cortinez's, affiliation was previously wrong and now corrected in this article.]

Summary

Mechanisms underlying loss of consciousness following propofol administration remain incompletely understood. The objective of this study was to compare frontal lobe electroencephalography activity and brainstem reflexes during intravenous induction of general anaesthesia, in patients receiving a typical bolus dose (fast infusion) of propofol compared with a slower infusion rate. We sought to determine whether brainstem suppression ('bottom-up') predominates over loss of cortical function ('top-down'). Sixteen ASA physical status-1 patients were randomly assigned to either a fast or slow propofol infusion group. Loss of consciousness and brainstem reflexes were assessed every 30 s by a neurologist blinded to treatment allocation. We performed a multitaper spectral analysis of all electroencephalography data obtained from each participant. Brainstem reflexes were present in all eight patients in the slow infusion group, while being absent in all patients in the fast infusion group, at the moment of loss of consciousness ($p = 0.010$). An increase in alpha band power was observed before loss of consciousness only in participants allocated to the slow infusion group. Alpha band power emerged several minutes after the loss of consciousness in participants allocated to the fast infusion group. Our results show a predominance of 'bottom-up' mechanisms during fast infusion rates and 'top-down' mechanisms during slow infusion rates. The underlying mechanisms by which propofol induces loss of consciousness are potentially influenced by the speed of infusion.

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Introduction

Loss of consciousness following induction of general anaesthesia is usually assessed clinically by assessing for response to verbal and/or physical stimuli [1], but this is often unreliable [2]. Following a typical induction bolus dose of propofol, loss of consciousness occurs rapidly, often within 10–15 s. In contrast, more gradual changes in consciousness can be achieved with slower propofol infusion rates. In both scenarios, it is assumed that loss of consciousness occurs as a result of a single mechanism and therefore it represents a unique neurobiological endpoint, where the speed of administration only changes the time to reach unconsciousness and not the mechanisms by which this endpoint is achieved [3].

Anaesthetic drugs generate dose-dependent changes in electroencephalographic (EEG) activity, which have been traditionally described as a slowing in the electroencephalogram oscillations at higher doses [4–8]. In recent decades it has been possible to describe the characteristic EEG patterns of commonly-used anaesthetic drugs [6, 9, 10]. In addition, it has been possible to obtain important information regarding the anatomical brain regions and neural dynamics affected by each drug and the biological mechanisms responsible for the loss of consciousness during general anaesthesia [11–13]. Despite these advances, the mechanisms underlying the loss of consciousness secondary to propofol administration remain incompletely understood.

Two mechanisms have been postulated [14]. The first is the 'bottom-up' mechanism, which is a predominance of brainstem suppression as the primary basis for the unconsciousness state. The counterpart is the 'top-down' mechanism, which refers to the loss of cortical integrative capacity for unconsciousness [14]. We hypothesised that different infusion rates, which will achieve different peak concentrations, will induce loss of consciousness predominantly through one mechanism or the other. We compared frontal EEG activity and brainstem reflexes during propofol induction of general anaesthesia in patients receiving a typical fast bolus dose (fast infusion) vs. a slow infusion.

Methods

We performed a parallel group, single-blind, randomised controlled trial with 1:1 randomisation to either a fast or slow infusion group. We received approval from the Institutional Ethics Committee (Clínica Alemana, Universidad del Desarrollo, Santiago, Chile), and written informed consent was obtained from all participants. We recruited ASA physical status-1 patients who were aged 18–65 years and scheduled to undergo elective hip arthroscopy. Patients with a history of neurological disease, history of substance or alcohol abuse, psychotropic drugs administration within 48 h before study procedures and documented adverse reactions to propofol were not included.

Randomisation was performed using a random number generator on the program SPLUS (TIBCO Software Inc. Palo Alto, CA, USA) by the study coordinator. Clinical outcome assessments were performed by a single neurologist (IA) who was blinded to study group assignment.

Participants assigned to the fast infusion group received propofol intravenously by target-controlled infusion (TCI) to a calculated effect-site target of 5.4 $\mu g.ml^{-1}$. The TCI was performed with the Marsh model (ke0 1.21 min^{-1}) at a maximum infusion rate of 1200 $ml.h^{-1}$. This target was selected since it represents the ED_{95} for unconsciousness [15] and was maintained constant for 10 min. Subjects assigned to the slow infusion group received propofol intravenously at a constant rate of 10 $mg.kg.h^{-1}$ until loss of consciousness. Propofol administration was then changed to TCI mode, using the same Marsh model, in order to maintain the predicted effect-site concentration observed at the point of loss consciousness as the target for 10 min. For both infusions, a TCI pump (Primea Orchestra™, Fresenius-Kabi, Germany) was used. No other drugs were administered during the study period.

Loss of consciousness was defined as the absence of eye opening and motor response to standardised verbal, tactile and painful stimuli (trapezius muscle pressure). Loss of brainstem reflexes was defined as the absence of pupil and corneal reflexes. These assessments are incorporated into the full outline of unresponsiveness (FOUR) score [16]. Neurological assessments were performed immediately before the commencement of the allocated propofol infusion speed and every 30 s after commencement.

The EEG data were obtained from four frontal electrodes using the SedLine™ monitor (Masimo Corporation, Irvine, CA, USA) at a sampling frequency of 89 Hz channel. DC offset removal was done by subtracting the mean of each channel activity to the actual signal of the channel. The EEG time series for each channel were then band pass filtered between 0.1 Hz and 44 Hz. For each channel, signal values greater than five standard deviations from the mean were considered as noise and subsequently rejected. Time frequency decomposition using the multitaper method was done using Chronux toolbox (http://www.chronux.org). Window length was 8 s with a 50% overlap. We used a time-bandwidth product of five. The

spectral power was normalised using the median value of the power during the baseline period, and power units were converted into decibels. The time profile for each frequency band power was obtained by averaging the power for each frequency in a specific band.

Spectral estimation was performed for each participant separately and was later averaged across all participants. The time of loss to verbal response was considered to be time zero. The analysis included EEG signals beginning 1 min before (baseline) and 1 min after commencement of propofol. The spectrograms were normalised using the median of the baseline period. Spectral analysis was focused on the alpha activity (8–12 Hz) and its change around loss of consciousness time in the fast and slow infusion groups. In order to perform this analysis, we computed the average mean power for the alpha band across all participants. We then compared the time profile of this band between conditions. All EEG analyses were conducted using Matlab 2016 (Mathworks, Natick, MA, USA).

The effect size was calculated to compare the alpha band time profiles between conditions. Calculations were performed with the software G*Power 3.1.9.2 (http://www.gpower.hhu.de). In order to obtain an effect of size of 1.995, we calculated that eight participants would be required in each group (assuming two-sided testing with a level of significance of 0.05 and a power of 80%). Comparisons between alpha band power time profiles were performed with a non-overlapping sliding window Wilcoxon rank sum test and corrected using a false discovery rate. A Fisher's exact test was used to compare the presence or absence of brainstem reflexes evaluated by the FOUR score between groups. Comparisons between continuous variables were performed with paired Student's t-test or the Wilcoxon signed rank test according to their distribution. A p value of less than 0.05 was considered statistically significant.

Results

Between 30 August 2016 and 12 December 2016, we included a total of 16 participants. The median (IQR [range]) time to loss of consciousness was 10.5 (9.2–15.4 [6.3–18.8]) minutes in the slow infusion group and 1.4 (1.4–1.5 [1.4–1.6]) minutes in the fast infusion group (p = 0.010). Predicted effect-site concentrations at loss of consciousness were 2.6 (2.5–3.0 [2.1–3.2]) $\mu g.ml^{-1}$ in the slow infusion group, and 4.6 (4.4–4.8 [4.1–5.2]) $\mu g.ml^{-1}$ in the fast infusion group (p = 0.010). The cumulative amount of drug given until the moment of loss of consciousness was 1.67 (1.49–2.70 [1.05–3.25]) $mg.kg^{-1}$ in the slow infusion group and 1.91 $mg.kg^{-1}$ in the fast infusion group (Table 1).

Brainstem reflexes were present in all eight participants in the slow infusion group, while being absent in all eight patients in the fast infusion group, at the moment of loss of consciousness (p = 0.010). Different EEG frontal patterns were observed in the spectrogram across participants during the induction of anaesthesia period in both groups (Fig. 1). Although an increase in alpha band power was observed before loss of consciousness in the slow infusion group, alpha power emerged several minutes after loss consciousness in the fast infusion group. Figure 2 shows the comparison of time profiles of alpha band power between the fast and slow infusion groups.

Discussion

Our study demonstrates that the speed of propofol infusion, during induction of general anaesthesia, determines the underlying mechanism through which loss of consciousness is achieved. Our results show a predominance of 'bottom-up' mechanisms during fast infusion rates and 'top-down' mechanisms during slow infusion rates.

The observed increase in alpha power that preceded loss of consciousness in the slow infusion group is in keeping with previous studies that reported increases in

Table 1 Baseline characteristics of participants receiving a slow or fast infusion of propofol. Values are median (IQR [range]) or number.

	Slow infusion n = 8	**Fast infusion n = 8**
Age; years	37(25–45 [23–55])	40 (25–57 [29–60])
Sex; male	4	6
Weight; kg	79 (59–91[58–95])	80 (74–90 [53–92])
Height; cm	173 (160–181[160–189])	175.5 (165–176 [160–180])
Time to loss of consciousness; min	10.5 (9.2–15.4 [6.3–18.8])	1.4 (1.4–1.5 [1.4–1.6])
Predicted effect-site concentrations; $\mu g.ml^{-1}$	2.7 (2.5–3.0 [2.1–3.2])	4.6 (4.4–4.8 [4.1–5.2])
Cumulative amount of drug; $mg.kg^{-1}$	1.67 (1.49–2.70 [1.05–3.25])	1.91

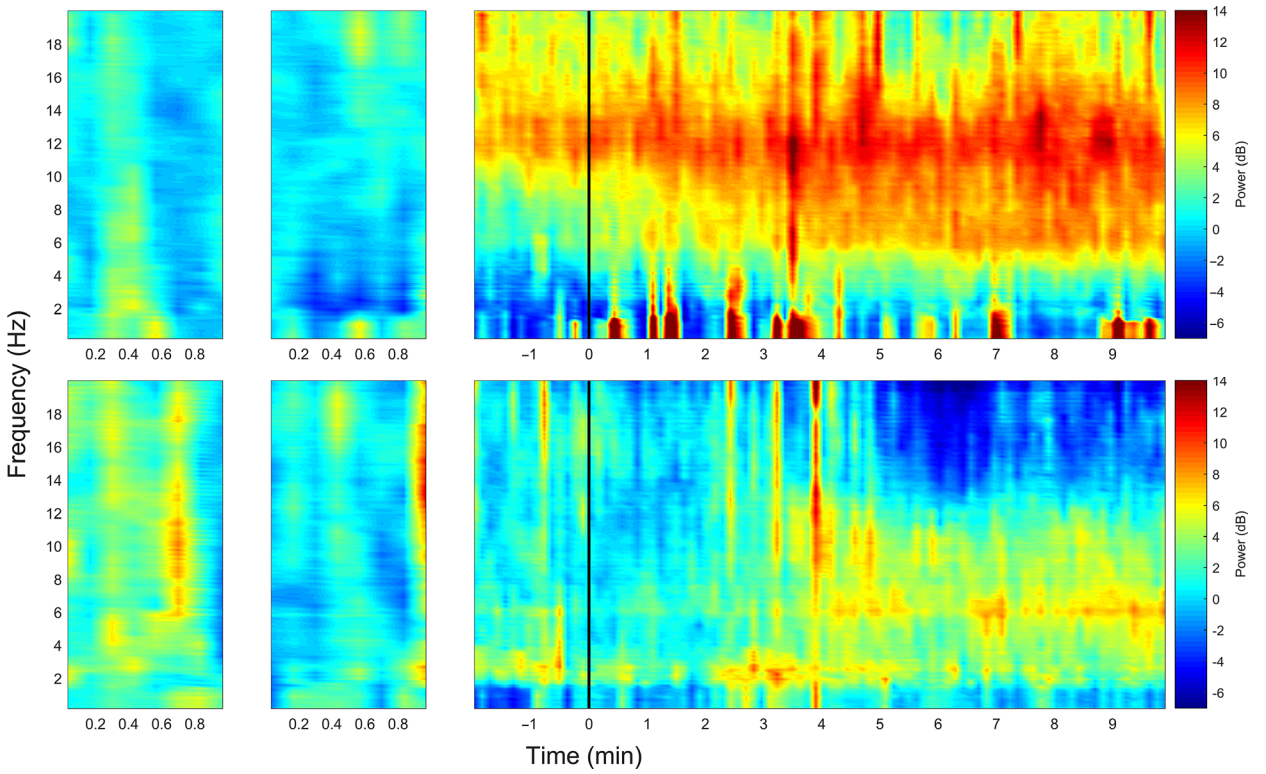
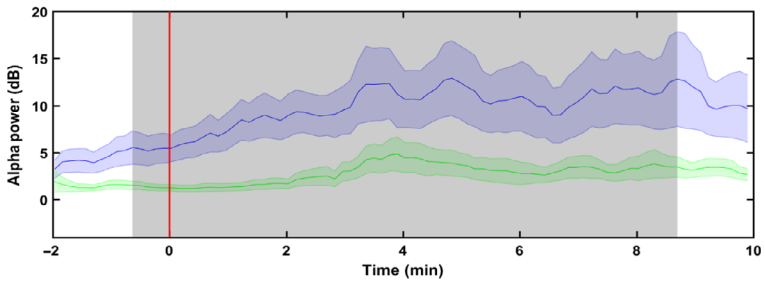


Figure 1 Average time frequency chart at baseline, administration start and zero-locked to loss of consciousness for a representative channel (R1). Top panel: time frequency chart for the slow infusion group; Bottom panel: time frequency chart for the fast infusion group. One minute of baseline (left), the first minute after commencing propofol and loss of consciousness (2 min before loss of consciousness and 10 min after loss of consciousness) periods are shown. The vertical black lines in the time frequency charts represent the times at which loss of consciousness occurred. An increase in alpha power is clearly observed at the point of loss of consciousness in the slow infusion group. In contrast, the emergence of alpha power occurs a few minutes after loss of consciousness in the fast infusion group.

frontal alpha to gamma power bands before loss of consciousness [9], and subsequent increases in the bifrontal coherence of the alpha bands during loss of consciousness following propofol administration [6, 17, 18]. The existence of frontal alpha power following propofol administration is thought to result from an increase in thalamocortical synchrony above the observable levels during wakefulness [19]. The



window	1	2	3	4	5	6	7	8	9
p value	0.049	0.004	0.001	0.007	0.037	0.020	0.037	0.037	0.065

Figure 2 Time slice of average alpha band power across subjects for slow infusion (blue) and fast infusion (green) groups. Shaded bars correspond to standard error and black shaded surface corresponds to significative differences between time slices. Red line indicates the time when loss to verbal response occurred. Data are shown from a representative channel (R1).

occurrence of this phenomenon diminishes or inactivates the functional coupling between regions that maintain consciousness [6, 17, 20]. The presence of frontal alpha power bands strongly suggests that loss of consciousness was achieved by the action of propofol on cortico-thalamic dynamics in the slow infusion group [17]. In addition, slower administration of propofol does not appear to significantly affect subcortical structures since brainstem reflexes were preserved in all participants [21]. The 'bottom-up'/'top-down' hypothesis supports the idea that loss of consciousness is the result of the activation, and not the depression, of deep brain structures related to awareness and sleep [22] Alternatively, 'top-down' mechanisms imply modulation of the cortical and thalamocortical circuits involved in the integration of neural information [14]

In contrast, the abolition of brainstem reflexes was consistently observed in all participants in the fast infusion group. This could be due to the action of propofol on brainstem nuclei at relatively high concentrations [23, 24]. Stimulation of inhibitory GABA-ergic nuclei, such as the ventrolateral preoptic nucleus, results in the inhibition of serotonergic and monoaminergic activating networks of the brainstem [23, 24]. The late appearance of a stable alpha band during the fast infusion scheme can be explained by a slower dynamic profile of the thalamic response [25, 26]. Although speculative, it is also possible that part of this delay may be explained by the instability of the mixing phase of propofol after the bolus dose. Another possible explanation for the abolition of brainstem reflexes could be due to a rapid dose of propofol producing more profound EEG suppression than a slow titrated induction and, therefore, differences between both groups could be explained by an overshoot of EEG suppression.

We observed that the predicted effect-site concentrations at loss of consciousness were much higher in the fast infusion group, when compared with the slow infusion group. Our data suggest that the use of effect-site concentration, at loss of consciousness after a fast induction using the Marsh PK model with a ke0 of 1.21 min^{-1}, cannot be recommended as a maintenance guide since it would lead to overdosing. Our results support slow infusion rates as being safer and perhaps more efficacious, based on clinical assessment of loss of consciousness and their correlated changes in frontal alpha power. The slow infusion approach would be important to consider in elderly patients, with aged or damaged cortical activity and minimal functional reserve, in whom excessive anaesthesia generates a greater risk of cardiovascular complications, delirium and postoperative cognitive dysfunction [27, 28]. The safety and efficacy of slow infusions, compared with the usual practices of bolus injections, should be prospectively tested in a clinical trial.

Our study has limitations. Different EEG monitors have been developed to measure cerebral hypnotic drug effect [29] but they do not provide fast and accurate information to detect transitions between the conscious and unconscious states [1, 7]. The delay times in the calculation of these indexes are a recognised limitation of current monitors to provide accurate real-time information of observed EEG changes [30]. In addition, different frontal EEG patterns at loss of consciousness during slow and fast propofol infusion rates observed in the current study may also limit the interpretation of these indexes during anaesthesia induction. We only studied healthy patients which limits the applicability of our results to other age groups or frail patients. In addition, we used the Marsh PK model with a ke0 of 1.21 min^{-1} to maintain stable effect-site concentrations after loss of consciousness for 10 min. Targeting effect-site concentrations within the current model might not necessarily translate into an immediate and constant effect [31].

In summary, the mechanisms through which propofol achieves loss of consciousness during induction of general anaesthesia are potentially influenced by speed of infusion. Our results support the predominance of 'bottom-up' mechanisms during the fast infusion rates and 'top-down' mechanisms during the slow infusion rates.

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